Novel thioglycosides towards chemoselective glycosylations

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Novel Thioglycosides Towards Chemoselective Glycosylations

Submitted by Philip Raymond Perkins

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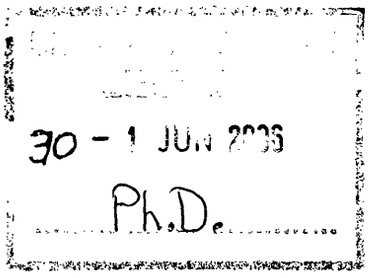
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Abstract

Carbohydrate chemistry has undoubtedly been one of the most researched areas of Organic Chemistry, spanning more than 200 years. Today research in the area produces a phenomenal amount of publications based on structural, physical and synthetic aspects of Carbohydrate chemistry. Today the number of synthetic methodologies available to the organic chemist is immense allowing the construction of a large number of biologically important oligosaccharides. Even with all this there is still no single technique by which all glycoside coupling combinations can be achieved, which remains one of the biggest challenges to the sugar chemist.

This thesis describes the synthesis of a series of new thioglycosides and their use as glycosyl donors, and their selective activation towards glycosylation using metal based Lewis acids.

This thesis comprises three main chapters, the first is a review of some of the major areas of modern glycoside synthesis, including mechanistic and stereochemical issues resulting from oligosaccharide synthesis. The second chapter describes the synthesis of a series of novel thioglycosides, their analysis, and their use in Lewis acid mediated glycosylation reactions and comparisons in reactivity with several known and well established techniques for the activation of thioglycosides. The second chapter also describes our attempts towards the synthesis of 1-*C*-glycosides. The final chapter reports the experimental procedures employed for each glycoside synthesised.

Abbreviations

Ac	Acetyl
AIBN	α,α'-Azoisobutyronitrile
All	Allyl
App.	Apparent
aq.	Aqueous
Ar	Aromatic
BDA	Butane-2,3-diacetal
Bn	Benzyl
b.p.	Boiling Point
br	Broad
BLM	Base Line Material
Bu	Butyl
Bz	Benzoyl
C	Celsius
CAN	Ceric ammonium nitrate
Cat.	Catalytic
CDA	Cyclohexane-1,2-diacetal
Cm	Centimetres
Conc.	Concentrated
Cp	Cyclopentadienyl
m-CPBA	*meta*-Chloroperbenzoic acid
CSA	Camphorsulfonic Acid
d	Doublet
DCE	Dichloroethane

DCM	Dichloromethane
dd	Doublet of doublets
Deg	Degrees
DHP	Dihydropyran
DHQD	Dihydroquinidine
DIBAL	Diisobutylaluminium Hydride
Dil.	Dilute
DMDO	dimethyl dioxirane
DME	Dimethoxyethane
DMF	*N, N*-Dimethylformamide
DMSO	Dimethylsulfoxide
e.e.	Enantiomeric Excess
EI	Electron Impact
eq.	Equivalents
ESI	Electrospray Ionisation
Et	Ethyl
FAB	Fast Atom Bombardment
Fru	Fructose
FYR	Furfuryl
g	Grams
GC	Gas Chromatography
Glc	Glucose
h	Hour
HIV	Human Immuno Virus
Hz	Hertz

i	Iso
IDCP	Iodine Dicollidene Perchlorate
IR	Infra Red
M	Multiplet
m	*meta*
MALDI-TOF	Matrix Assisted Laser Desorption Ionisation – Time of Flight
Man	Mannose
Max.	Maximum
Me	Methyl
Mg	Milligrams
Min.	Minutes
MHz	Megahertz
ml	Millilitres
mmol	Millimoles
mol	Moles
mm	Millimetres
m.p.	Melting point
n	Normal
NIS	*N*-Iodosuccinimide
Nm	Nanometres
NMR	Nuclear Magnetic Resonance
nOe	Nuclear Overhauser Effect
o	*ortho*
p	*para*
Ph	Phenyl

Piv	Pivaloyl
PMB	*para*-Methoxybenzyl
ppm	Parts per Million
Pr	Propyl
Pyr.	Pyridine
q	Quartet
R	Unspecified Carbon Group (substituent)
RT	Room Temperature
s	Singlet
sept	Septet
t	Triplet
t	Tertiary
TBAF	Tetrabutyl ammonium fluoride
TBDPS	*tert*-Butyldiphenylsilyl
TES	Triethylsilyl
Tf	Trifluoromethanesulfonate
THF	Tetrahydrofuran
THIO	Thiophenyl
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
X	Unspecified Heteroatom

Nomenclature and Numbering

The graphical representation of stereochemistry which is used in this thesis was initially proposed by Maehr.[1] The representation of absolute stereochemistry is depicted by the use of bold and broken wedges whilst representation of relative stereochemistry of racemic compounds is given by the use of bold and broken lines. Bold wedges on conformational representations indicate proximity to the viewer and signify the material is of a single enantiomeric form. If broken lines are widened this represents an increase in distance from the viewer. In addition to this where an anomeric ratio is expected or observed a waved line is used.

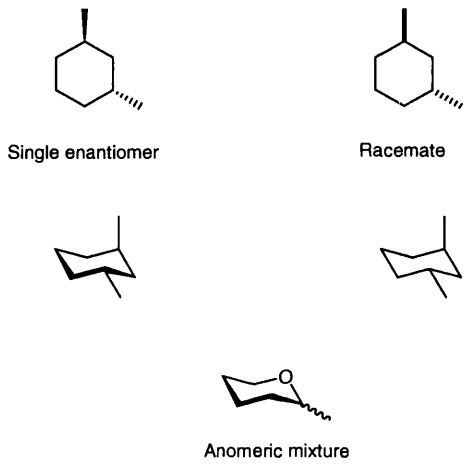


Figure 1: *Stereochemical representations*

Carbohydrate nomenclature

The naming of carbohydrate compounds is complex and so there are numerous texts which detail the precise rules for the naming of monosaccharides.[2,3] There are several key pieces of information given within the name of a given saccharide; for example, from the name of a saccharide used frequently in this thesis 'methyl-α-D-mannopyranoside' the following information about the structure of the compound can be obtained:

The 'methyl' prefix describes the substituent configuration of the anomeric 1-oxygen and the 'manno-' portion gives the relative stereochemistry of the remaining hydroxyl groups (i.e. the particular series to which the compound belongs).

The symbol D shows which enantiomeric form is present relating to the stereochemistry at highest asymmetric hydroxyl group.

The α prescript indicates the relative configuration of the anomeric substituents and is dependant upon the stereochemistry of the highest asymmetric carbon in a pyranose or fuanose ring system. If the substituent at the anomeric centre lies on the opposite face of the ring system to the highest asymmetric carbon then it is designated the α anomer. The term pyranoside indicates that the saccharide exists in the six membered ring form.

Higher sugars which possess more than one stereogenic centre will have stereoisomers which are not related as object and nonsuperimposable mirror images i.e. they are diastereoisomers. The definition of α and β configurations and thus the D and L forms is relative to the stereochemistry of the highest numbered asymmetric centre. The carbon atoms are numbered from the aldehyde terminus (C-1) counting along the chain C-2, C-3 etc. As a result tetroses have two diastereomeric pairs of enantiomers called erythrose and threose and each pair is diastereomeric with the other. Their absolute configuration is determined as mentioned by the taking into account the configuration at C-3 and whether this is the same as that for D or L glyceraldehyde. Classically the terms threo and erythro describe the relative configurations of two adjacent stereogenic carbons (fig2).

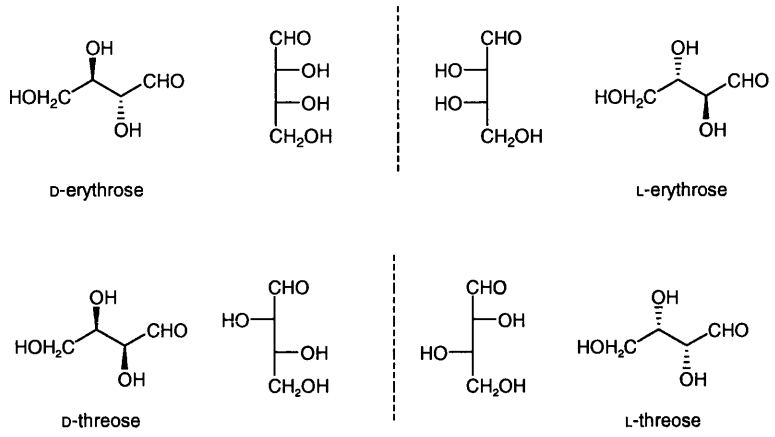


Figure 2: *Diastereomeric relationship of erythrose and threose*

The majority of saccharides depicted in this thesis have an α configuration when the anomeric substituent is in an axial orientation. Numbering of monosaccharides in this thesis begins at the anomeric carbon as 1 and anomeric proton as 1 as seen in (Figure 3).

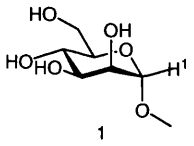


Figure 3: *Nomenclature and numbering of monosaccharides*

There are a couple of different ways in which glycosidic linkages are classified. The first of these relates to absolute configuration of the C-1 and C-2, which includes the 1,2-*cis* and 1,2-*trans*-2-D-glycero series (allo, gluco, gulo and galactopyranosides) and the 1,2-*cis* and 1,2-*trans*-2-L-glycero series (altro, manno, ido-, and talo galactopyranosides) (Figure 4). Alternatively glycosidic linkages can be classified according to two criteria. Firstly the composite monosaccharides are described, secondly the linkage positions of firstly the glycosyl donor and then the acceptor are employed for example Sucrose (Figure 4) (a disaccharide essential in the diets of animals originating from cane or beet sugar), comprises of two monosaccharide components D-glucose and D-fructose linked to the anomeric position of glucose i.e.

C-1 of glucoside connected to C-2 of fructose would be described as Glc(1→2)Fru (Figure 4).

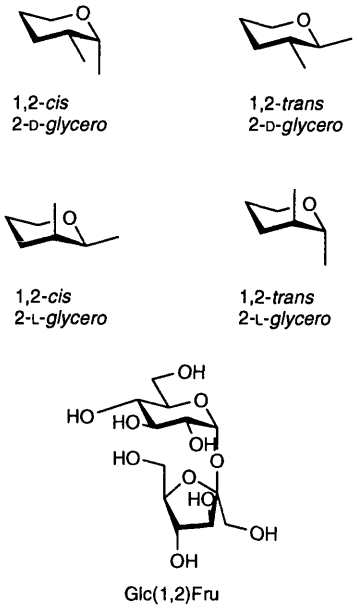


Figure 4: *Types of anomeric linkages*

Chapter 1

1 Introduction

1.1 Aims, Reasons, and Challenges in Carbohydrate Chemistry

Carbohydrate chemistry is arguably one of the largest single areas of synthetic organic chemistry, and probably the most published area in existence. To this end the aim of this introduction is not to cover the countless works of the enormous number of research groups which have made contributions to the vast knowledge of carbohydrate chemistry that is present in the literature, but to highlight some of the important features which have been discovered certainly over the past thirty or so years. Another important aim is to describe to the general reader how difficult carbohydrate chemistry can be, exemplified by the fact that there is still no general method for the generation of any given glycosyl linkage.

Carbohydrates are among the most abundant and diverse classes of compounds present in nature. Although their major importance is in biological systems, carbohydrates are also important in many other areas including the food, clothing and agrochemical industries. This abundance and apparently endless number of practical uses has driven chemists for the past one hundred and fifty years; from the pioneering work by Emil Fischer towards the end of the 1800s on the parent monosaccharides,[4] the basic building blocks on which this whole family of compounds is based, to the development of techniques available for the routine synthesis of complex oligosaccharides and glycoconjugates (Figure 5) in the modern laboratory.[5,6]

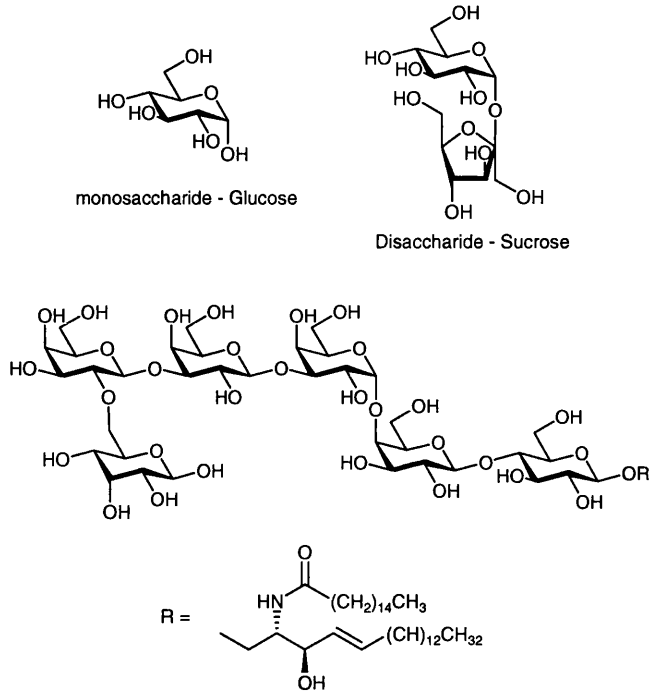


Figure 5: *Types of glycosides*

Carbohydrates are found as monomers, oligomers, polymers and components of biopolymers. They have also been shown to display many integral roles bestowing certain chemical, physical and biological properties upon carrier molecules and have been implicated in major roles governing cellular processes such as cellular transport devices, cell-cell division and recognition. Today there are many hundreds of varying techniques available for selective synthesis of specific target saccharides, but even armed with such techniques there is still a considerable desire towards the generation of simpler more stereoselective methods by which any given linkage between saccharides can be made.

The high demand for the selective synthesis of complex oligosaccharides makes carbohydrate synthesis a significantly more complex operation than that for other branches of organic chemistry. Taking the condensation reaction between three amino acids as an example, there are only three product combinations possible, however, if you consider three identical hexoses there are over 1000 different

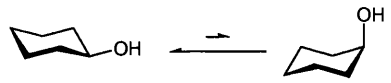
combinations by which the three can be linked together. Nevertheless, modern carbohydrate chemistry allows the possibility of as many as twenty plus monosaccharides to be linked together by the execution of complex multi-step synthetic procedures. Such a synthetic strategy is obviously subject to limitations even with today's advances in the field, namely that the strategy needs to be convergent, with particular priority being given to the production of the relevant glycosyl donor and acceptors for each glycosylation step in the synthesis. Furthermore, it is also necessary to limit the number of synthetic steps and each step is required to be not only high yielding but also stereoselective.

In conclusion, although research within the biological and synthetic carbohydrate community has progressed hugely in the field over the past one hundred and fifty years, there is still an ever present need to satisfy the global need for complete and straightforward control over the synthesis of complex carbohydrate molecules.

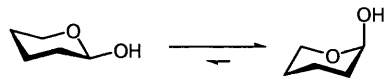
1.2 Principles in carbohydrate chemistry

1.2.1 The Anomeric effect

The anomeric effect is a stabilising effect which results in a preference for an electronegative substituent to orientate itself in an axial position rather than the predicted equatorial position, when positioned in the 2-position of a tetrahydropyran (THP) ring. [7,8] The well documented preference for a chair conformation in six-membered ring systems implies that the axial arrangement would be less favoured through 1,3-diaxial steric interactions, which is indeed the case for cyclohexanol. However in the case of THP, there is a considerable difference in the relative energies of the axially and equatorially orientated electronegative substituents in the 2-position resulting in the axial position being favourable (Figure 6).



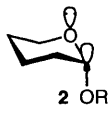
Cyclohexanol example:The preference for the equatorial arrangement of the hydroxyl substituent, minimises1,3-steric diaxial interactions.



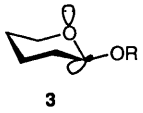
THP shows a thermodynamic preference for the hydroxyl to be axial

Figure 6: *Steric and thermodynamic preference for substituent configuration*

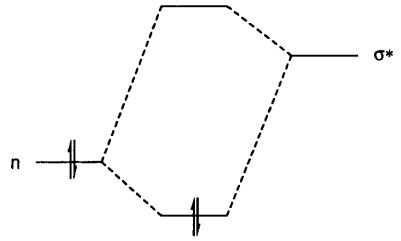
This difference is rationalized by the consideration of the extra stabilisation obtained when orbital overlap occurs between the lone pair of the ring oxygen and the σ* orbital of the exocyclic bond in **2** (Figure 7). The electronegativity of the substituent is crucial, as this is responsible for a lowering in the energy of the unoccupied σ* orbital to such an extent that it is possible for the orbital to overlap efficiently with the lone pair orbital of the ring oxygen. Considering the alternative conformation **3** where the electronegative substituent lies equatorially to the ring, it is clearly illustrated that the overlap of the relevant orbitals is 'spacially' not allowed for this scenario as the major lobe of the equatorial bond is not suitably aligned (Figure 7). The energy difference between the axial and equatorially substituted cases has been calculated to be 1.4 kJ mol^{-1}.



Antiperiplanar relationship
overlap symmetry allowed



Orbitals not aligned
overlap symmetry forbidden



Overlap of lone pair (n) orbital with accessible, vacant σ* orbital leads to stabilisation

Figure 7: *The Anomeric Effect in molecular orbital terms*

If the electronegative substituent possesses a lone pairs of electrons itself, overlap may also occur in the opposite direction. As these lone pairs of electrons are able to rotate about the axis of the exocyclic bond, unlike those of the ring oxygen, it is however important to note that a stabilising interaction only occurs in certain conformations. This is the 'so called' *exo*-anomeric effect (Figure 8) and leads to a single favoured conformation for the exocyclic electron withdrawing group. In the case of dispiroketal's, which have been extensively studied and published by Ley and co-workers[8-11] these two types of anomeric effects are indistinguishable due to the fixed conformations within the structure of the two THP rings and the dioxane.

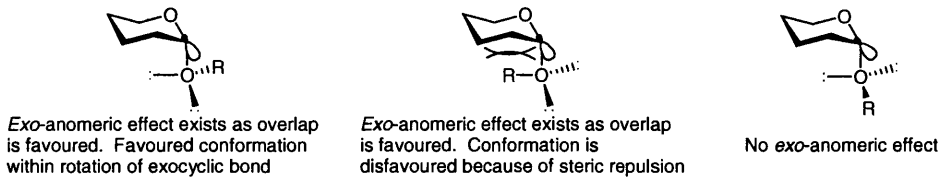
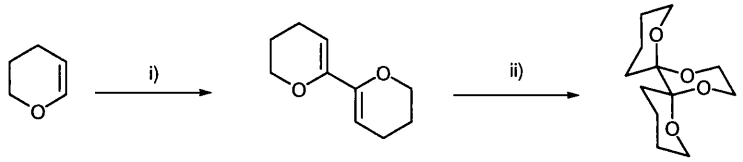


Figure 8: *Axial Anomeric Effect*

Appling the thermodynamic conformational preferences of systems, which posses multiple anomeric effect possibilities, dispiroketals are convenient substrates to illustrate the fact that the system will maximise the number of *exo*-anomeric effects in its preferred conformation (Figure 9). Thus, the thermodynamic preference for the maximisation of anomeric effects proves sufficient to control the relative configuration of the acetal centres. Subsequent production of the *bis*-dihydropyran and reaction with ethyleneglycol is outlined in (Scheme 1).



Reagents and conditions : i) *t*-BuLi, THF then cat. $PdCl_2(PPh_3)_2$, $CuCl_2$, 0°C;
ii) Ethylene glycol, Cat. CSA, toluene, reflux.

Scheme 1: *The BHP protection protocol*

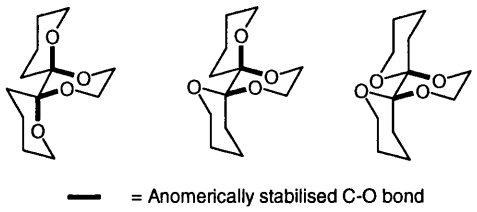


Figure 9: *The cumulative dominance of the Anomeric Effect*

Another key feature to the selectivity of the reaction is the minimisation of 1,3-diaxial interactions when forming the dioxane ring of the dispiroketal (Figure 9). The dioxane ring also shows a preference for an all chair array which controls the selectivity of these systems and is also highly useful in their use as protecting groups. The presence of side chains is also governed thermodynamically by their presence in the preferred equatorial position which prevents repulsive 1,3-steric interactions which are possible with the dispiroketal protecting group. As a result of this, any axially orientated side chain equilibrates to the corresponding equatorially positioned dispiroketal **5** (Figure 10) by a deketalisation then re-protection protocol under reversible acetal hydrolysis/formation conditions.

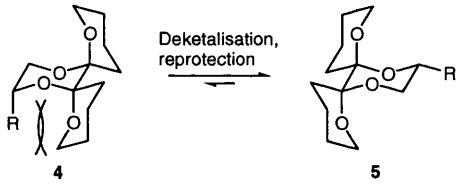
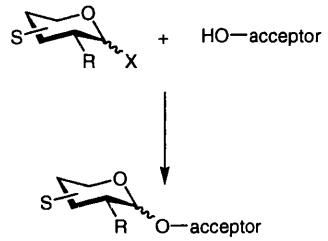


Figure 10: *Deketalisation equilibrium*

In conclusion the anomeric effect therefore has a profound influence on the thermodynamic determination of conformations in systems such as carbohydrate glycosidic bonds and protecting group selectivity, and will play a key role later in discussion points in this thesis.

1.2.2 Principles of glycosidic bond formation

Glycoside synthesis is usually considered to be accomplished by the condensation reaction between a fully protected glycosyl donor which bears a suitable leaving group at the anomeric centre, and a suitably protected glycosyl acceptor containing one free hydroxyl group (Scheme 2), although in this introduction there will be highlighted examples of chemoselective glycosylations where the donor and acceptor contain other hydroxyl functionality and the reaction proceeds *via* either a chemoselective or regioselective driving force.



Scheme 2: *Principles of glycosylations*

There are several factors which are known to affect the α:β ratio in glycosylation reactions; the substituent in the C-2 position **R** can be designed to participate in the reaction mechanism giving opposite anomeric results to that which may be intuitively expected. The orientation of **R** may also influence the anomeric outcome of a given glycosylation. The types of substituents **S** present on either the donor or acceptor may also play a part in stereoselevtivity based on, for example, sterics or merely due to their relative positions (axial vs. equatorial). Many numerically enriched procedures have been developed utilising specific properties of a given glycosyl donor's leaving group. The type of promoter system has also been shown to influence the α:β ratio of many glycosylation procedures. The solvent used may also play an important part in the reaction mechanism, whilst pressure and temperature can also allow discrimination against kinetic and thermodynamically favoured products for a particular glycoside series. These factors will be discussed in this

chapter as they all play an integral part in the chemistry of a particular reaction system.

Historically the most widely used glycosylation strategies have used anomeric halides as glycosyl donors.[12-14] These compounds however have been known to suffer from instability and require relatively drastic reaction conditions during their preparation, apart from glycosyl fluorides which are stable to deprotection of *O*-protected glycosyl acetates and are widely used today.[15] The use of orthoester and imidate based donor systems were amongst the first attempts at providing alternative glycosylation methodologies. The generation of these types of donors has led to an upsurge in the development of new glycosyl donors to offer the organic chemist (Figure 11). Of these, the most popular have been the glycosyl fluorides **6**, trichloroacetimidates **7**, thioglycosides **8** and selenoglycosides **9** which, can be prepared and then reacted under mild conditions.

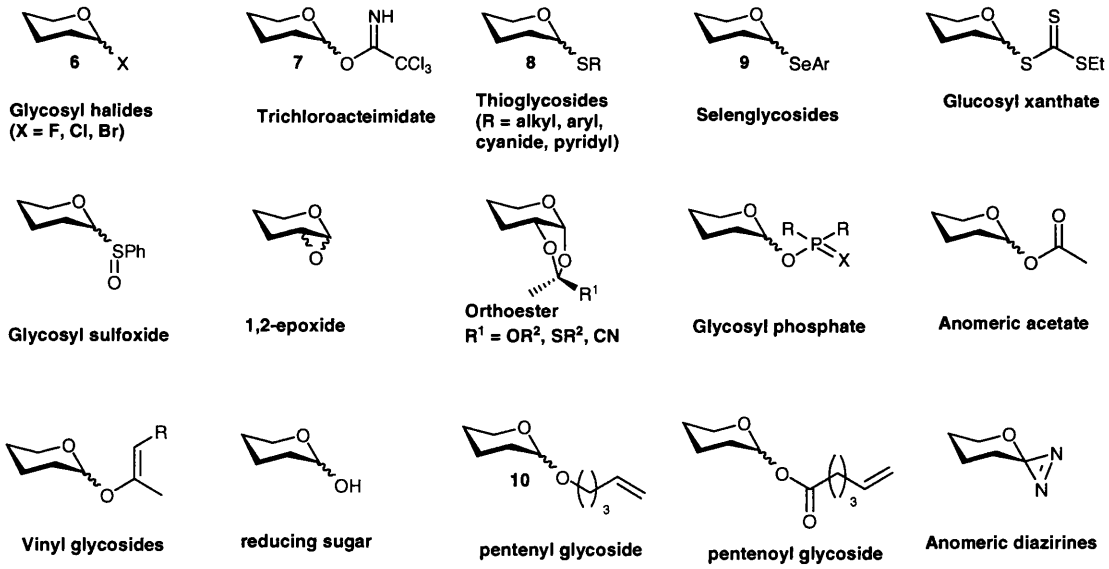
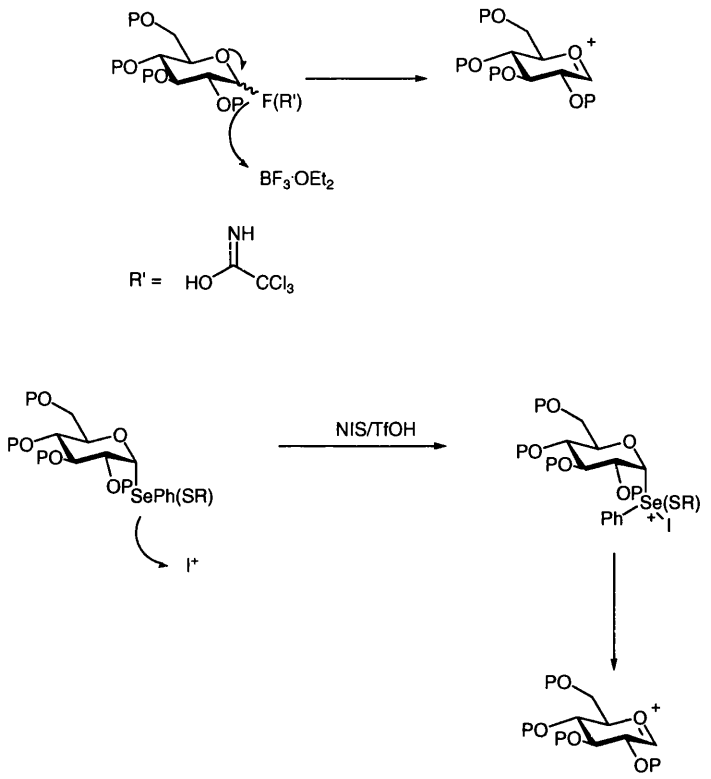


Figure 11: *Types of glycosyl donor*

Glycosyl fluorides and indeed the trichloroacetimidates are easily activated by treatment with the Lewis acid $BF_3{\cdot}OEt_2$ and glycosylation proceeds with the addition of an appropriate glycosyl acceptor. Thioglycosides and selenoglycosides are both

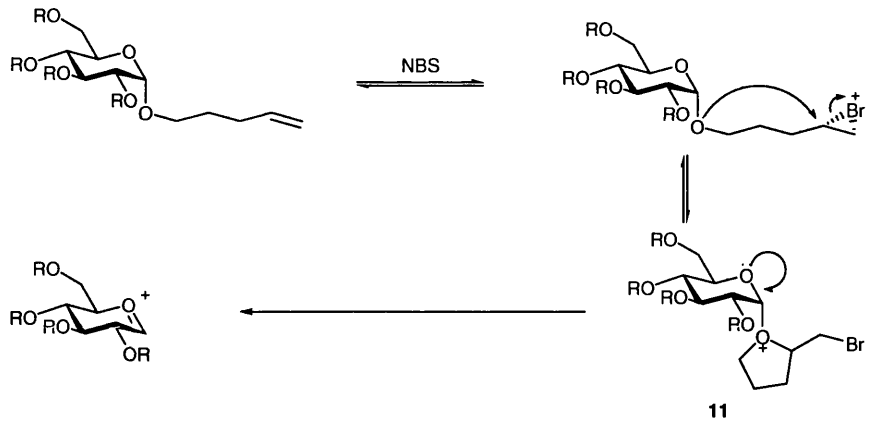
activated by the addition of *N*-iodosuccinimide and triflic acid (NIS/TfOH) (Scheme 3).



Scheme 3: *Activation of glycosyl fluorides and selenoglycosides*

N-Pentenyl glycosides are useful glycosyl donors because of their inactivity under a wide range of activating conditions. Also, due to their properties as an *O*-glycoside, they can be activated by conversion to a better leaving group. This is achieved by the addition of a suitable halide electrophile donor such as *N*-bromosuccinimide (NBS), iodonium dicollidine perchlorate (IDCP) or IOTf (which is generated by the addition of NIS with TfOH *in-situ*).

The electrophilic halonium ion generated under the activation conditions results in activation of the terminal double bond forming a second cyclic halonium ion at the terminus of the pentane fragment. The anomeric oxygen then traps this cyclic halonium ion forming a cyclic oxycarbenium ion intermediate **11** which is now a good carbohydrate donor leaving group (Scheme 5).



Scheme 4: *Activation of pentenyl glycosides*

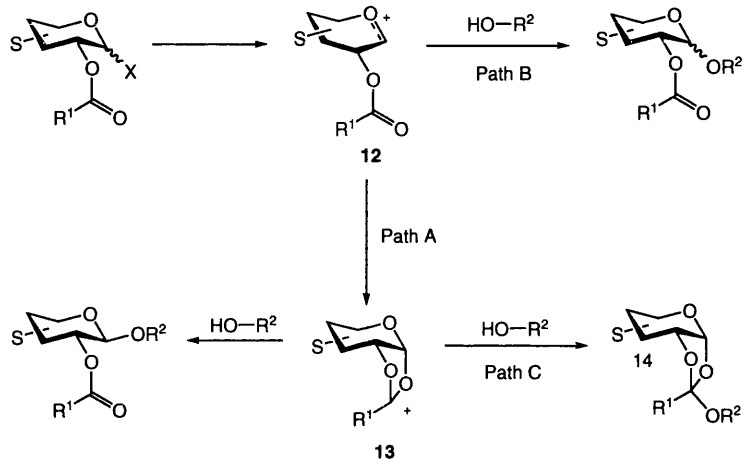
These compounds have offered improved stability with regards to purification and have been shown to be stable in storage for a considerable period of time. The appropriate choice of reaction conditions has also given rise to high yields and high α:β selectivities. The selective introduction of a glycosidic linkage has been and continues to be one of the key challenges within oligosaccharide synthesis.

1.3 Neighbouring group assisted procedures

Careful selection of the protecting group at the C-2 position can considerably effect the selectivity at the anomeric centre of a given glycosylation procedure. A protecting group at C-2, which can participate during a glycosylation process, allows the construction of 1,2-*trans* glycosidic linkages. The stereoselectivity of a non-participating C-2 protecting group strategy will be determined by the reaction conditions (e.g. solvent, temperature, and promoter). In this situation the functionality of the glycosyl donor (barring C-2) and acceptor (e.g. leaving group of the donor, type of saccharide protection and substitution pattern), will play a major part in α:β selectivity.

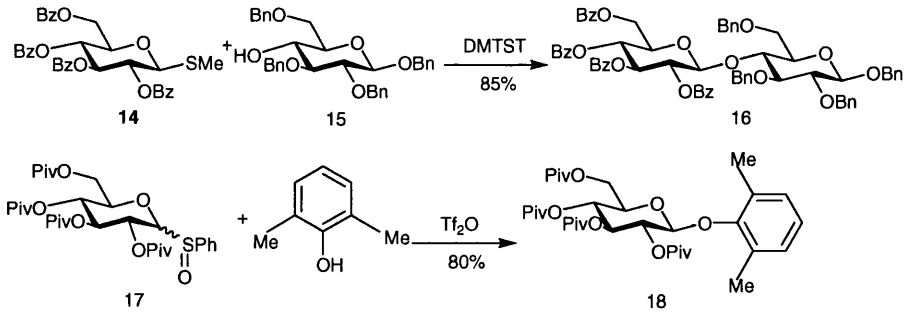
Neighbouring group assisted procedures are most reliably performed using C-2 acyl functionalities (Scheme 5). Activation of the anomeric centre resulting in the formation of an oxonium ion **12** is common to both routes. Attack of the anomeric

carbon by the 2-*O*-acetyl group (Path A) results in the formation of a more stable acetoxonium ion **13**, nucleophilic attack upon the anomeric centre by the glycosyl acceptor then results in the formation of a 1,2-*trans* glycosidic linkage. Direct attack of the oxonium ion (Path B) at this point occurs for systems where the attack of the acceptor is favoured over acetoxonium ion formation.



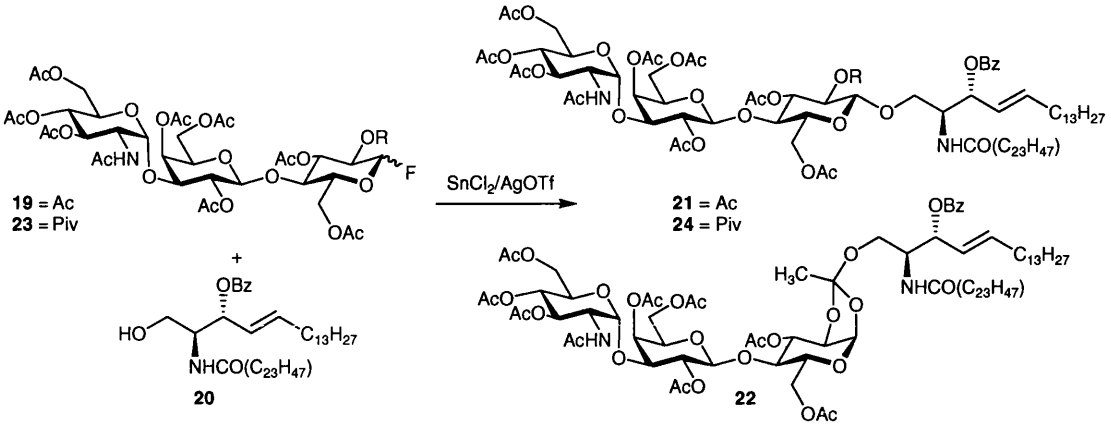
Scheme 5: *C-2 assisted glycosylation strategy*

When the donor is a glucosyl based donor the result is a β-linked glycoside, whilst mannoside type donor systems will give α-glycosides due to the conformation of the 5 membered acetoxonium ring being directed by the equatorial C-2 oxygen. This also directs subsequent ring opening from the β face in the case of the glucoside based donors. The use of C-2 participating groups has also been shown to be compatible with a number of different glycosyl donors.[16,17] Selected examples are illustrated below (Scheme 6). The coupling of methyl thioglycoside **14** with C-4 unprotected glycosyl acceptor **15** in the presence of DMTST gave the expected disaccharide product in a 85% yield; whilst coupling of pivaloyl (PIV) protected glycosyl sulfoxide donor **17** with 2,6-dimethylphenol in the presence of triflic anhydride gave coupled product **18** in 80% yield. This again shows the versatility of this process.



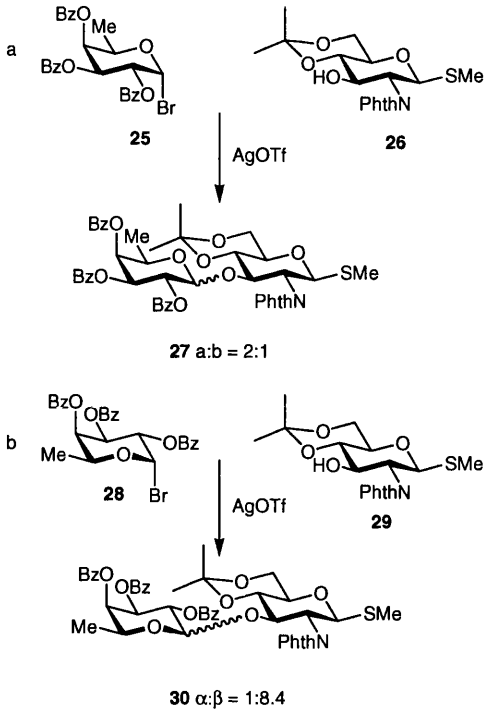
Scheme 6: *Examples of C-2 assisted glycosylations*

The literature precedent reveals examples of glycosylations where the alcohol acceptor attacks the C-2 position of the dioxolane ring **13** resulting in the formation of the undesired orthoester by-product [18] (Path C) (Scheme 5) For example reaction of glycosyl donor **19** with acceptor **20** gave only trace amounts of coupling product **21** and a significant amount of the orthoester **22**. Careful design of the corresponding glycosyl donor has allowed this problem to be overcome, thus the use of donor **23** under the same reaction conditions gave glycoconjugate **24** in 77% yield (Scheme 7). In this donor the 2-*O*-acetyl protecting group was replaced with a trimethylacetyl (pivaloyl) protecting group (Scheme 7). The diversion of the reaction mechanism towards favouring the glycosylated product can be rationalised as follows: formation of the orthoester is disfavoured due to the presence of the bulky *tert*-butyl group adjacent to the carbonyl carbon, which increases the reactivity at the anomeric centre. This effect is also mimicked when benzoyl protecting groups are utilised.



Scheme 7: *Nucleophilic attack of orthoesters*

There have been cases reported where the use of a participating C-2 group and glycosylation proceeds *via* the usual oxonium ion **12** but provides mixtures of anomers. For example, van Boeckel and co-workers demonstrated that the coupling of glycosyl bromide **25** with acceptor **26** in the presence of silver triflate at –50 °C gave disaccharide **27** with an anomeric ratio of α:β 2:1 (Scheme 8). The use of the benzoyl protecting functionality at C-2 should yield the β-glycoside product, in this case however the α-glycoside was formed in predominance. The hypothesis given for this is that the transition state leading to the β-glycoside is heavily disfavoured by steric hindrance between the benzoyl functionality and the phthalimide (PhthN) protecting group present at C-2 of the glycosyl acceptor. It was therefore predicted that the use of glycosyl donor **28** which possesses 'opposite chirality' should give rise to a different stereochemical outcome *via* double stereodifferentiation. This was observed when the coupling of glycosyl donor **28** with acceptor **29** under identical conditions afforded mainly the β-linked disaccharide **30** (α:β = 1:8.4) (Figure 12b).



Scheme 8: *Double stereodifferentiation*

Computational modelling of the transition states in this case correctly predicted that the transition state leading to β-product **31b** is the more favoured 'matched pair' (Figure 12).

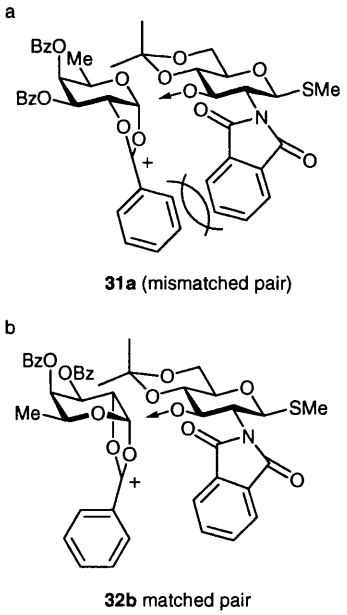


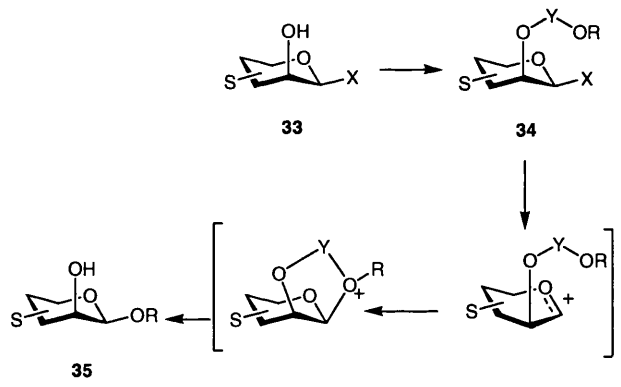
Figure 12: *Double stereodifferentiation a steric solution*

In conclusion where glycosylations using neighbouring group strategies give unexpected α:β ratios, unfavourable steric interactions in the transition state are the

most common cause. These can often be reduced by the use of less sterically demanding protecting groups.

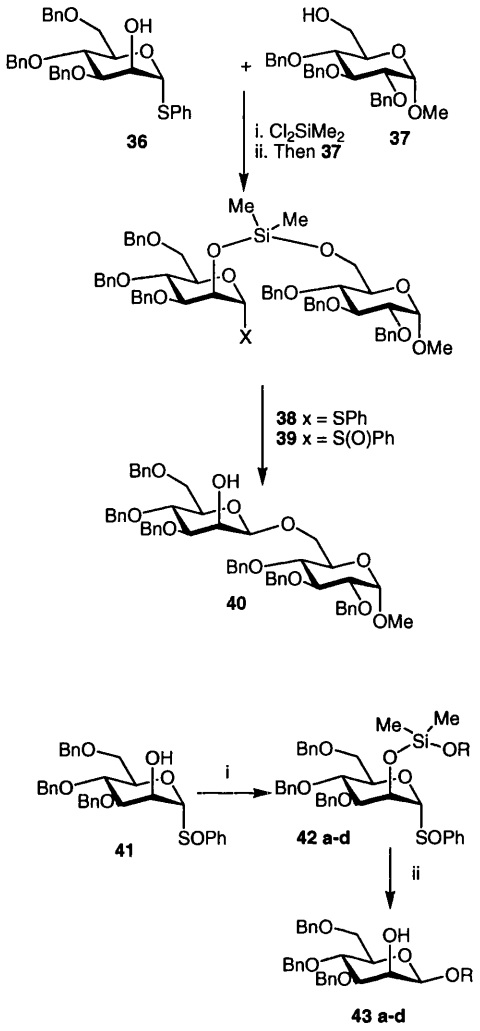
1.4 Intramolecular Aglycon Delivery (IAD)[19-24]

Intramolecular aglycon delivery has shown utility for the production of β-mannosides. This procedure relies on a sugar alcohol linked *via* the formation of an acetal or silicon *tether* (Y = CH_2 or $SiMe_3$) to the C-2 position of suitably protected mannose donor **33** (Scheme 9). Activation of the anomeric centre allows the aglycon to then be delivered selectively to the β-face of the glycosyl donor **34**, subsequent cleavage of the silicon or acetal tether from both the C-2 linkage and the acceptor fragment results in the synthesis of β-glycoside **35**.



Scheme 9: *Principles of Intramolecular Aglycon Delivery (IAD)*

Initially the groups of Stork et al.[25] and Hindsgaul et al.[26-28] were involved in the development of this elegant and selective strategy which led to several publications during the 1990's and reported the first stereo-controlled synthesis of β-mannosides by the use of a silicon tether. Further investigation into the methodology led Stork to modify the original protocol.[29-31] Initial studies involved activation of a thioglycoside **36**, to the corresponding sulfoxide **39**, after tethering of the silyl moiety of the acceptor (Scheme 10).

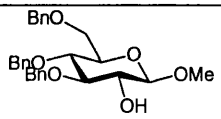
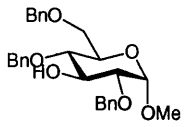


Reagents and conditions: i. R-OH, **32a-b**, imidazole, DMAP, Me_2SiCl_2, THF ii. Tf_2O, DTBP, ET_2O, DCM

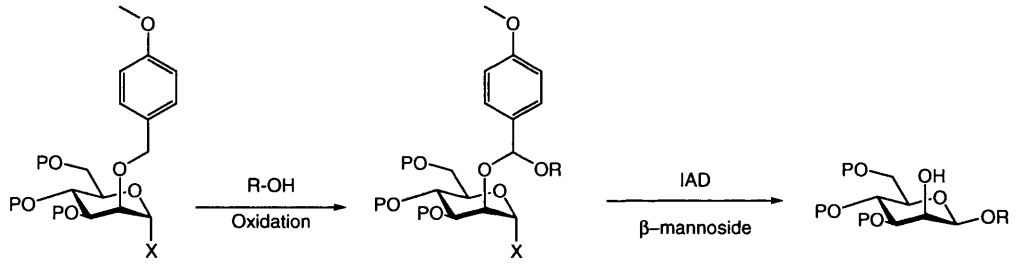
Scheme 10: *Examples of IAD*

The new strategy involved the attachment of the tether to the sulfoxide donor **27** resulting in a more dynamic synthesis of β-mannosides in generally good yields (Table 1).

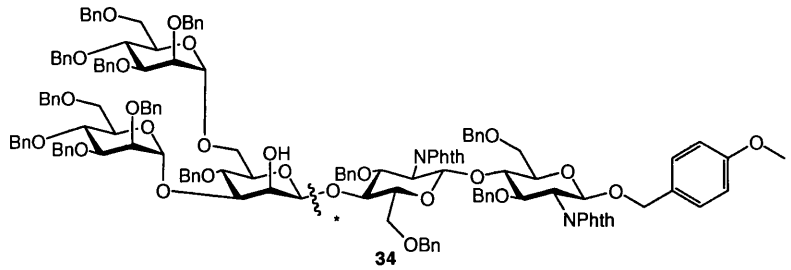
Table 1: *Selected examples of IAD*

	ROH 32	Tethering yield (%)	Glycosylation yield (%)	Overall yield (%)
A		84	65	55
B		88	82	72

Ogawa and co-workers[32,33] have reported the use of a *p*-methoxybenzyl assisted IAD strategy (Scheme 11) along with further modifications thereof to give an elegant synthesis of β-mannosides. In the strategy their key step is the β-mannoside linkage step in the synthesis of pentasaccharide **34** (Figure 13).



Scheme 11: *PMB based IAD procedure*

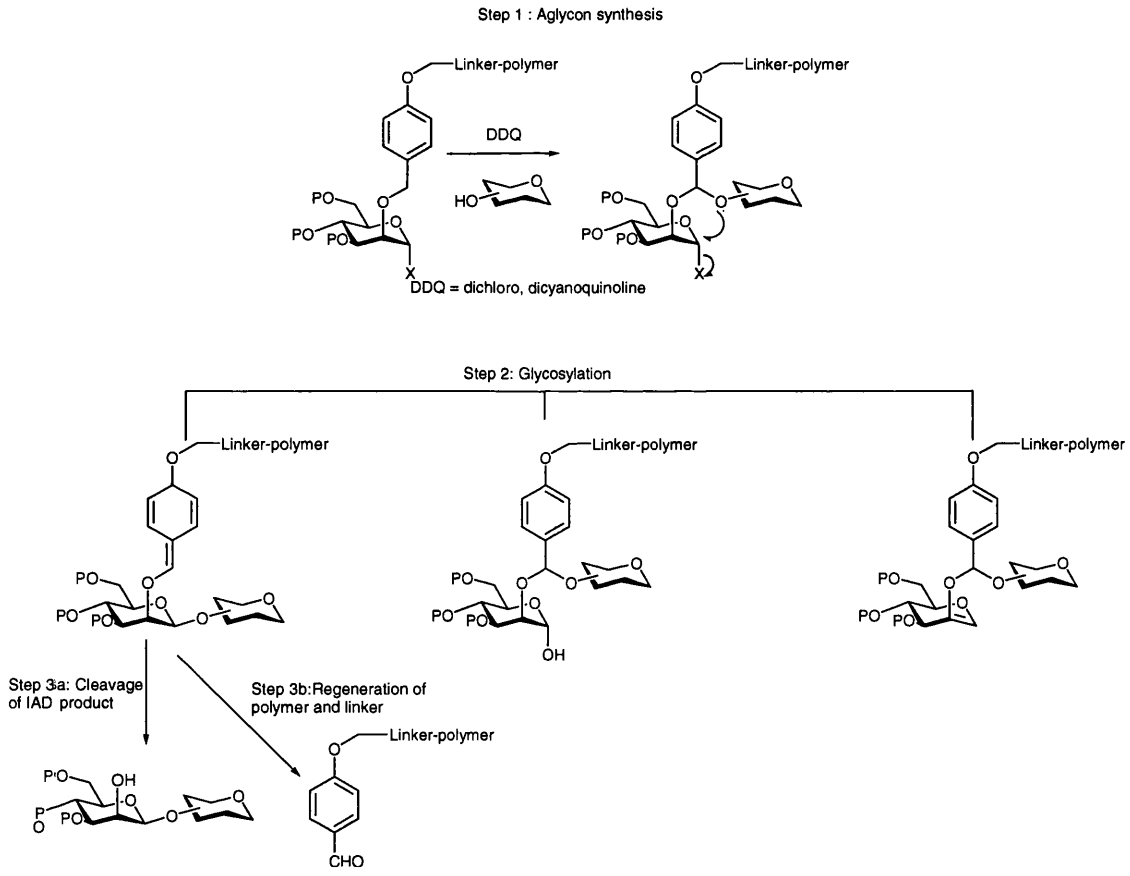


* - key β–mannoside linkage derived by Owgawa PMB methodology

Figure 13: *PMB based IAD target pentasaccharide*

In their expanded results they reported that glycosylation with a trisaccharide donor and an acceptor resulting from the retrosynthetic analysis of **34** above was said to proceed *via* the mixed acetal intermediate under the standard *p*-methoxy benzyl (PMB) assisted mannosylation conditions. Interestingly, this method has also been

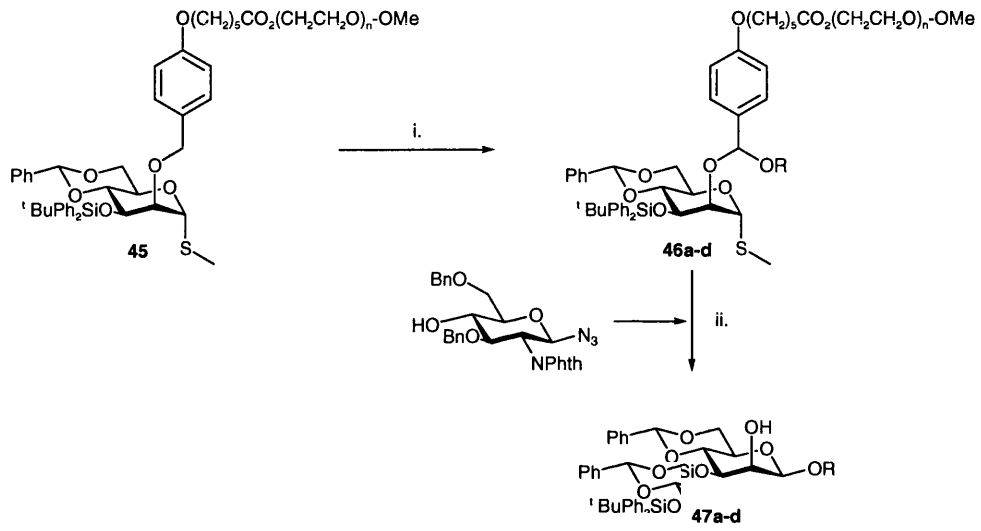
adapted to polymer support (Scheme 12)[34] with Ogawa demonstrating the PMB group's versatility in producing β-mannosides which was previously unprecedented. In their general three step approach, tethering glycosyl acceptor to the PMB type solid support occurs upon reaction with DDQ. The second step involves activation of the anomeric leaving group and the delivery of the tethered glycosyl acceptor. The final step in Ogawa's strategy involves cleavage of the IAD product and recycling of the polymer and linker. The added bonus for this strategy resulted from the ease of purification, because the required β-products can be cleaved from the polymer leaving undesired impurities still attached.



Scheme 12: *Polymer supported IAD using PMB strategy*

The polymer bound linker donors were prepared in a similar fashion to that of the usual 2-O-PMB derivatives, with all six steps proceeding in moderate to high yields.

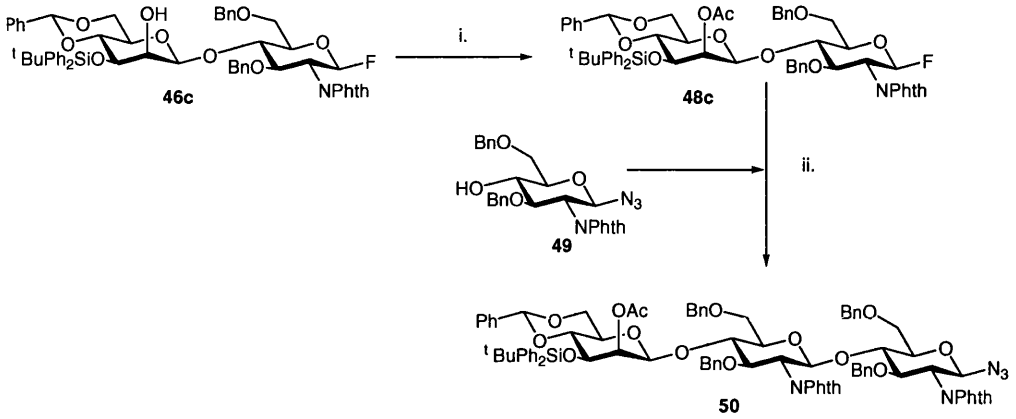
The utility of this method was first demonstrated using compound **45** (Scheme 13). Chemical shifts in the ^{1}H-NMR spectrum depicted that the mixed acetal **46a** was present as a single stereoisomer, which was precipitated with *tert*-butyl methyl ether (TBME) and followed by work up and simple chromatographic separation afforded β-mannosides exclusively in 50% yield. [34]



Reagents and conditions: i, ROH DDQ, 4 Å MS,CH_2Cl_2, rt, 3h, ii. MeOTf, DTBMP, 4 Å MS, DCE.

Scheme 13: *Specific example of polymer supported IAD*

This initial result demonstrated the potential for this IAD method *via* solid phase controlled conditions. Following this, the IAD glycosylation procedure was performed on glycosyl fluoride donor **46c**, which was coupled to the C-4 unprotected glucosyl azide donor **49** to give the orthogonally protected trisaccharide core of the *N*-linked glycoprotein **50** (Scheme 14).[35]

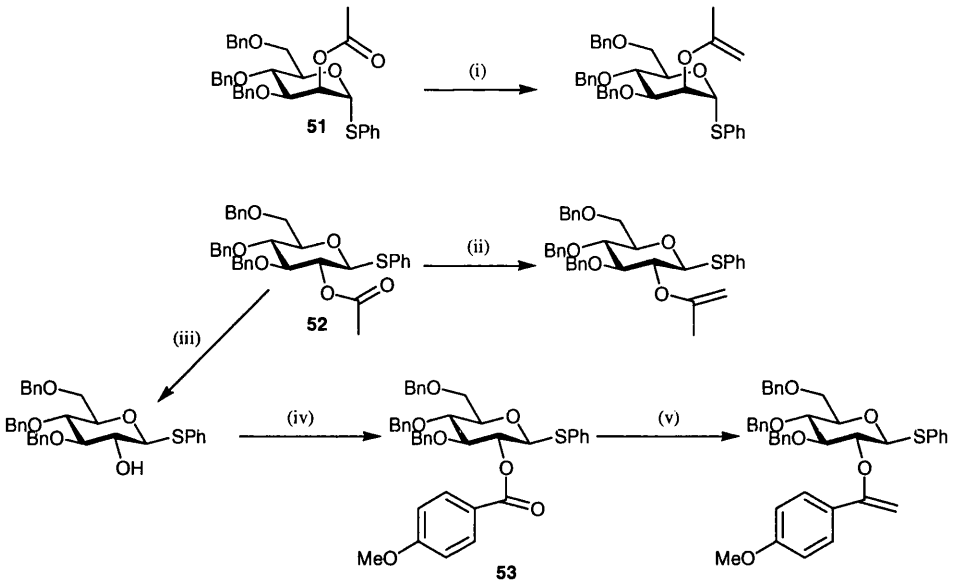


Reagents and conditions: i. Ac_2O, pyridine. ii. Cp_2HfCl_2,AgOTf, DCE, 49.

Scheme 14: *IAD towards N-linked glycoproteins*

This investigation has studied the stereochemical outcome of the tethering procedure showing that it indeed proceeds with a high degree of diastereofacial selectivity. There have been a number of modified IAD strategies but thus far they have not been as successful in forming β-mannosides as the PMB assisted procedure which includes the use of a C-2 PMB thioglycoside strategy by Fairbanks and co-workers (Scheme 15).[36]

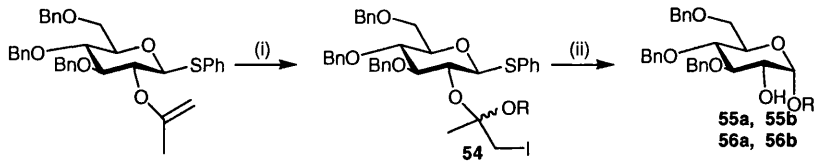
In their variation Fairbanks and co-workers combined Hindsgaul's mixed ketal approach. This approach initially showed limitations when 'bulky' aglycons were employed whilst Ogawa's PMB system does not suffer from this limitation. The use of *N*-iodosuccinimide mediated variants of acetate derived enol ether systems *via* a 'new hybrid Ogawa/Hindsgaul system' was achieved by Tebbe methylation of thioglycosides **51**, **52**, **53** of the 2-*O*-*para*-methoxybenzoyl protected glycosyl donor.[37]



Reagents and conditions. (i) Tebbe reagent, pyridine, THF, -40°C to RT,2h, 70%; (ii) Tebbe reagent, pyridine, THF, -40°C to RT,2h, 68%; (iii) Na, MeOH, RT, 18h, 94%; (iv) *p*-anisic acid, DCCI, THF, DMAP, reflux, 18h, 52%; (v) Tebbe reagent, pyridine, THF, -78°C to RT, 18h, 66%.

Scheme 15: *Extended IAD methodology*

Unfortunately for the PMB system, the mixed ketal **54** produced in the subsequent reaction with NIS and corresponding alcohols (Scheme 16) proved to be unstable to work up but did lead to a one pot strategy with overall glycosylation yields of 49% and 55% for methanol and diacetone galactose acceptors. Although sugar based alcohols proved successful substrates the secondary alcohol cyclohexane gave the only anomeric selectivity observed in their investigation (α:β = 3:1).



Scheme 16. (i) ROH, NIS (3 equiv.), THF, -78°C - RT; (ii) NIS (5 equiv.), DTBMP, CH_2Cl_2, 0°C to RT

Scheme 16: *IAD towards α-glycoside synthesis*

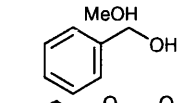
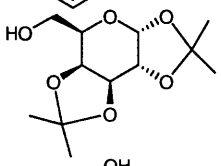
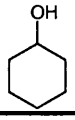
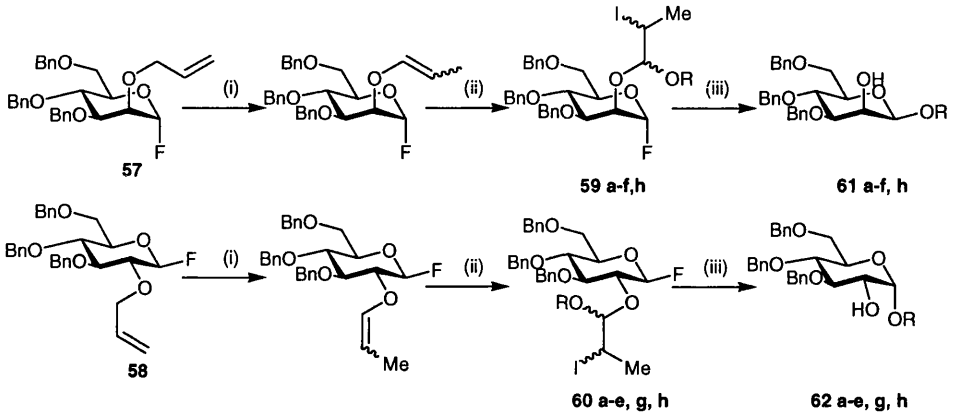
Entry	Acceptor ROH	Product/yield of mixed ketal	Product/yield of glycosylation
a)		**54a**/92%	**55a**/70%
b)		**54b**/66%	**55b**/88%
c)		**54c**/95	**56a**/63%
d)		**54d**/76	**56b**/quantitative

Table 2: *Selected IAD results for α-glycoside synthesis*

The encouraging element of this work was the further utilisation of a C-2 acetate functionality to control the anomeric outcome giving in both cases 1,2-cis glycosides for both the *gluco* and *manno* series. Fairbanks and co-workers[38] have also shown that different glycosyl donor types are compatible by demonstrating the use of glycosyl fluorides in this IAD strategy. The use of a 2-*O*-allyl protecting group with thioglycosides and fluorides has been investigated. The use of glycosyl fluorides **57** and **58** allows the tuning of the donor reactivity to induce a facile IAD process under differing activation conditions. The whole process is initiated by isomerisation of the allyl double bond with Wilkinson's catalyst, formation of the corresponding ketal intermediates **59** and **60**, using the usual NIS mediated method, followed by direct IAD under Lewis acidic conditions gives glycosylated products **61a-h** and **62a-h** respectively, selected results are shown in Table 3.

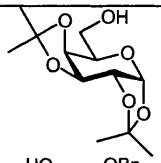
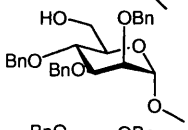
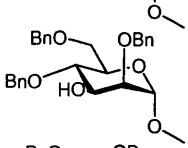
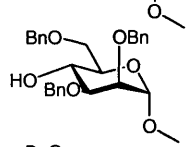
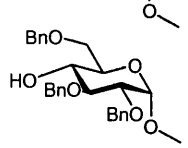
In the case where thioglycosides were used as the anomeric activating group their investigations with the use of hindered alcohols resulted in competing direct

anomeric activation giving unexpected anomeric ratios. This problem was overcome by the use of the glycosyl fluorides with $SnCl_2$ as the anomeric activator (Scheme 17).



Scheme 15. (i) Wilkinson's catalyst, ^{n}BuLi, THF, 70°C, 96%; man, 98%;glc; (ii) ROH a-h (Table XX) NIS, DCE, -40°C - rt, 4 A; (iii) AgOTf, DTBMP, $SnCl_2$, DCE, or MeCN, 50°C; then TFA, H_2O or NIS, H_2O.

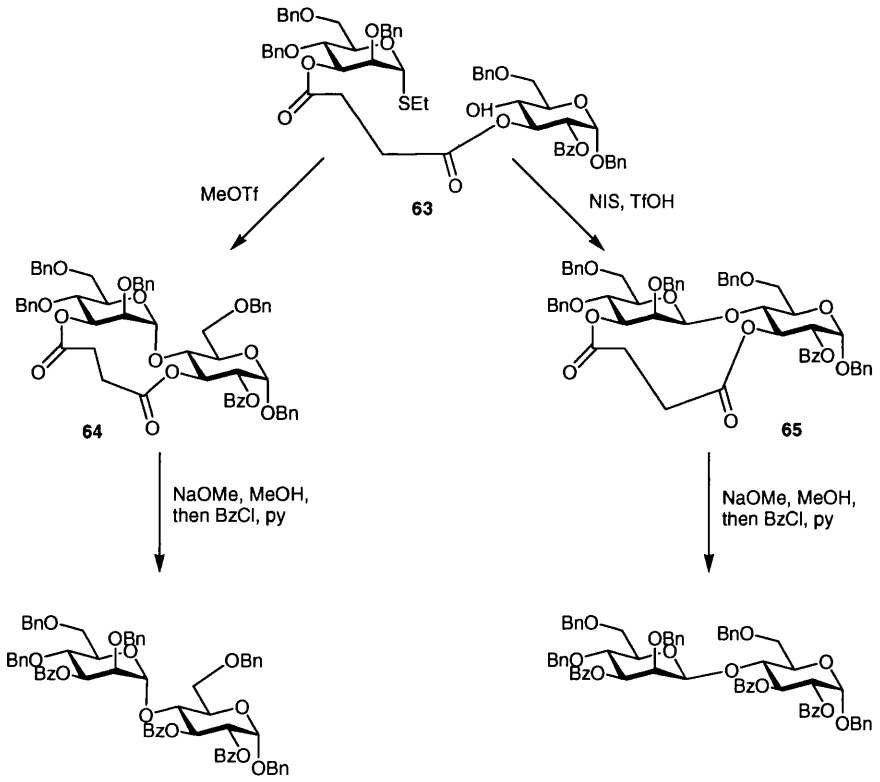
Scheme 17: *Allyl glycosides in IAD procedures*

Entry	Acceptor ROH	Product/yield of mixed ketal	Product/yield of glycosylation
a)		**59c**/98% **60c**/91%	**61c**/61%[d, f] **62c**/63%[d]
b)		**59d**/80% **60d**/79%	**61d**/49%, 75%[d] **62d**/44%, 46%[d]
c)		**59e**/83% **60e**/52%	**61e**/55%[d,f] **62e**/66%[d,g]
d)		**59f**/37%	**61f**/50%[d]
e)		**60g**/39%	**62g**/45%[d]

a Isolated yields are shown. Reactions carried out in DCE unless otherwise stated. b Reaction carried out in THF. c Isolated yields. Acid treatment with TFA except otherwise stated. d Reaction carried out in DCE. e Reaction carried out in acetonitrile. f No acid treatment. g Treatment with NIS, H_2O

Table 3:*Selected allyl IAD glycosylations*

Another important aspect of IAD is the fact that there is flexibility within the process in terms of choice of tethering position. Several groups have demonstrated that not only are different combinations of tethering possible for both the glycosyl donor and acceptor, but also that the choice of tethering position can in fact drastically effect the stereochemical outcome of the glycosylation reaction. Ziegler and Lemanski[39,40] have shown that when C-2 or C-6 succinoyl protecting groups are employed in mannosyl donors only moderate glycosyl selectivities were observed. Tethering to the C-3 hydroxyl positions of both the donor and acceptor glycosides **63** showed that high selectivities were possible for each anomeric outcome when different anomeric activators were used (Scheme 18). The use of MeOTf resulted exclusively in α-product **64** whilst the use of the alternative activation system NIS-TfOH gave predominantly β-product **65**. The ability to control the stereochemical outcome has proven to be the 'Holy Grail' for glycoside chemists worldwide.



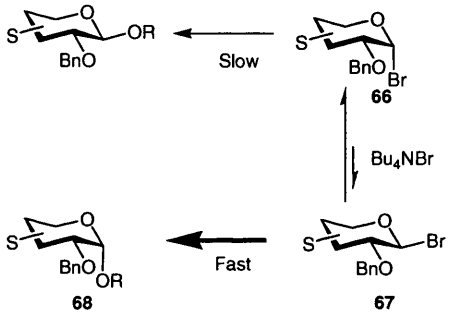
Scheme 18: *C-3 – C-3 disaccharide IAD protocol*

Ziegler has also demonstrated that the size of the tether is an important factor. When a C-6 succinoyl protected hydroxyl mannoside tether was used the anomeric selectivity was poor, however, decreasing the tether size by removing an ethylene group resulted in high selectivityies again with galactoside and glycoside acceptors, but continuing poor selectivity when a mannose acceptor was used. Lamanski's investigation of 'matching' and 'mismatching' of the four O-6 – O-6 tethers of both D and L glucose with D or L mannose, revealed that altering of the tethering point of the acceptor resulted in an alteration of the anomeric ratio from a ≈1:1 α:β to 100% α for the L-manno donor D-gluc acceptor pair. The reason for this is neighbouring group participation (NGP) from the C-2 tethered position. Also observed was that the L-rhamnose, D-gluc tethered pair gave a ≈1:4 α:β showing a preference for asymmetric induction *via* IAD over a NGP mechanism in this case. The use of succinoyl tethering of *O*-2 to *O*-3 glucosyl to glucosamine or glucoside gave α-selective glycosylation even when a C-2 acyl function was used. The use of a parallel O-2 to O-6 system though gave α:β mixtures.

1.5 In-situ Anomerisation[41]

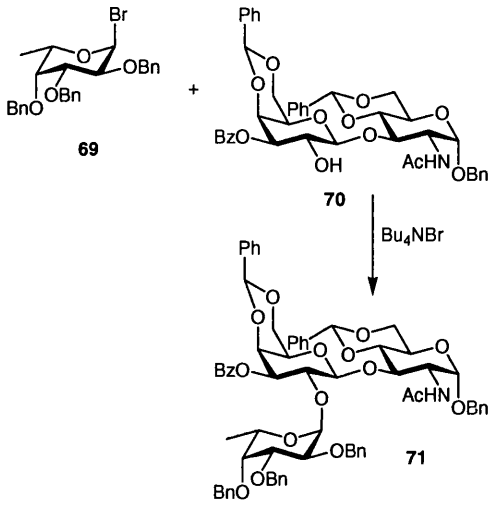
The discovery of *in-situ* anomerisation proved an invaluable technique in the generation of α-glycosidic linkages including the formation of α-glucosides which like the β-mannosides are notoriously difficult to form controllably. This technique requires glycosyl donors which do not possess a C-2 participating protecting group. The key process in this reaction is the development of a pre-equilibrium of the α- and β- halides, *via* a S_N2 inversion effected by the tetrabutylammonium bromide catalyst. This equilibrium is strongly biased towards the α-bromide which is stabilised by the anomeric effect.[7,8] The energy barrier for attack by the nucleophilic

alcohol is lower for the β-halide **67** and thus the S_N2 attack by the alcohol that results in the formation of α-glycosides **68** is dominant. The key requirement for this process is that the rate for the pre-equilibrium is much faster than the glycosylation process. Also important is the use of solvents with low polarities, due to the stabilisation of the oxonium ion formed in the traditional glycosylation process when polar solvents are used. In more demanding systems there is a need for stronger activating agents to be used and as a result a whole library of such systems has been developed.[42]



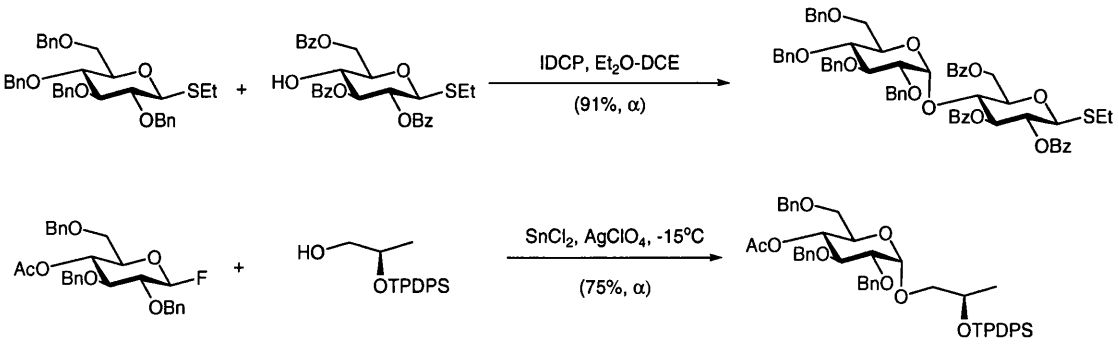
Scheme 19: *In-situ anomerisation*

In initial work Lemieux and co-workers[43,44] have described the coupling of bromide donor **69** with disaccharide acceptor **70** in the presence of tetrabutylammonium bromide which resulted in trisaccharide **71** predominantly as the α-anomer (Scheme 20).



Scheme 20: *Example of In-situ anomerisation*

The stereochemical outcome of this reaction can be explained by the Curtain-Hammett principle.[45] Tetrabutylammonium bromide itself is only successful at inducing anomerisation with very reactive substrates. Other examples of such systems are the use of trimethylsilyl triflate with perbenzylated trichloroacetimidate glycosyl donors which in many cases afford exceptional α-selectivities at low reaction temperatures, a reaction still in common use.[46-53] Other examples have reported the use of thioglycosides along with anomeric fluorides also giving high α-selectivities (Scheme 21). The reaction mechanism of these examples has not been studied in depth, but it is reasonable to presume that they do indeed proceed *via* an *in-situ* anomerisation.

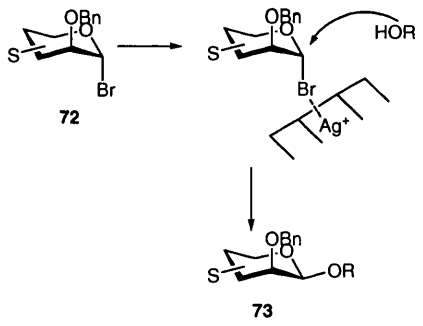


Scheme 21: *Alternative in-situ anomerisation*

As described earlier there are many factors which affect any particular glycosylation strategy and this is no exception for *in-situ* anomerisation or careful choice of donor, acceptor and reaction conditions are required to achieve good results.

1.6 Glycosylation with inversion of configuration

As discussed in the previous section *in-situ* anomerisation requires fast equilibrium between the α and β halide pair, other glycosylation strategies involve the inhibition of this equilibrium, allowing the glycosylation to proceed by a more S_N2 based reaction mechanism, resulting in the expected inversion of configuration. A classic example of this is seen when α-halide **72** in the presence of an insoluble silver salt results in the formation of mainly β-glycoside **73** (Scheme 22). [54-57] In the absence of suitable nucleophiles the anomerisation process is prohibited from occurring thus driving the reaction towards β-glycoside synthesis.



Scheme 22: *Glycosylation with inversion of configuration*

Silver silicate and silver aluminate have also been applied routinely as heterogeneous catalysts. These catalysts have been shown to produce β-linked mannosides due to the interaction between the axial orientated α-bromide functionality and the catalyst 'locking' the conformation of the bromide to an extent where glycosylation proceeds in an S_N2 type fashion. Usually in the case of mannosides there is a preference for α-linked mannosides due to a combination of the anomeric effect and the steric

effects of any C-2 functionality. So as 1,2-*trans* products usually predominate any method where β-mannosides are formed is extremely valuable.

The presence of a non-participating C-2 function is also a prerequisite when using a heterogeneous catalyst. Van Boeckel and co-workershave also demonstrated that the nature of the substituents at C-3, C-4 and C-6 have significant importance on the outcome of a particular glycosylation reaction. Scheme 23 shows the reaction between bromide **74** and C-4 unprotected acceptor azide **75** to afford the dimer **76** as a mixture of anomers. [58-60] When the acetyl group at C-3 was replaced with a benzyl group **77** disaccharide **78** was isolated predominantly as the β-anomer. Reaction with the glycosyl donor possessing a trichloroacetyl group at C-3 **79** also gave a dimer **80** as a mixture of anomers. When a series of experiments were run with glycosyl donors bearing C-4 acyl **81** and C-4 trichloroacetyl protected bromide **83**, high β-selectivities were seen in disaccharides **82** and **84**. The use of a C-4 alkyl protected group in glycosyl bromide (**85**) resulted in disaccharide **86** with lower anomeric selectivity. From these results it was concluded that the presence of an acyl group at C-3 decreases β-selectivity whilst at C-4 the inverse is true.

74 R^1 = Ac; R^2 = Bn
77 R^1 = R^2 = Bn
79 R^1 = $COCCl_3$; R^2 = Bn
81 R^1 = Bn; R^2 = Ac
83 R^1 = Bn; R^2 = $COCCl_3$
85 R^1 = Bn; R^2 = allyl

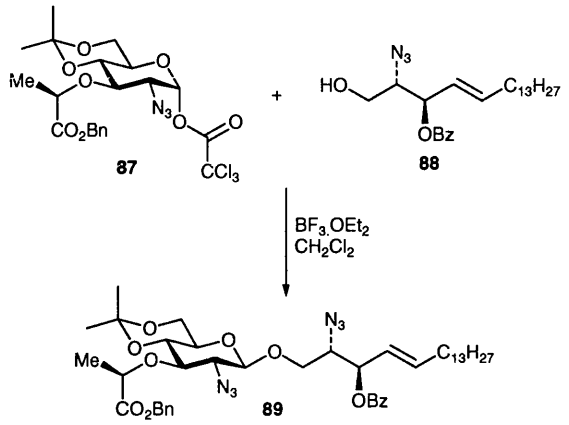
75

76 R^1 = Ac; R^2 = Bn; α:β = 1:1
78 R^1 = R^2 = Bn; α:β = 1:6
80 R^1 = $COCCl_3$; R^2 = Bn; α:β = 1:1
82 R^1 = Bn; R^2 = Ac; α:β = 1:9
84 R^1 = Bn; R^2 = $COCCl_3$; α:β = 1:10
86 R^1 = Bn; R^2 = allyl; α:β = 1:5

Scheme 23: *Examples of glycosylations with inversion*

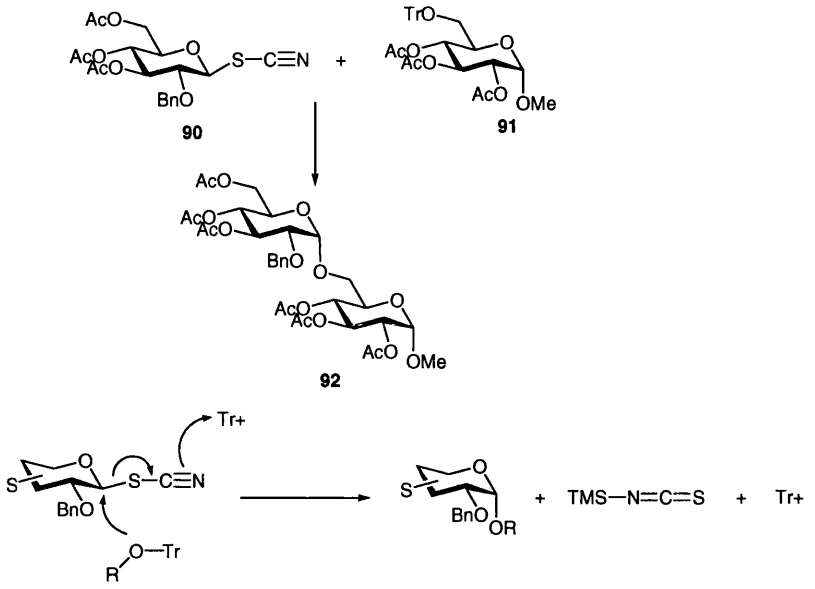
Glycosylations may proceed *via* inversion when apolar solvents and mild Lewis acids are employed. Schmidt and co-workers [61] have shown that the use of $BF_3{\cdot}OEt_2$ promoted glycosylation of α-glucosyl and α-galactosyl trichloroacetimidates in dichloromethane or dichloromethane-hexane mixtures gave mainly β-glycosides. In

their example α-trichloracetimidate **87** was coupled with acceptor **88** by use of $BF_3{\cdot}OEt_2$ in DCM to give the coupled product **89** with high β-selectivity (Scheme 24).



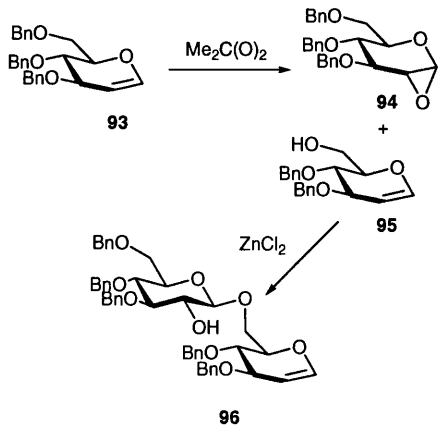
Scheme 24: *Trichloroacetimidates in inversion protocols*

Another novel example of a glycosylation with inversion of configuration has been developed by Kotchetkov and co-workers.[62,63] In their approach the aim was the synthesis of 1,2-*cis* pyranosides by reaction of 1,2-*trans*-glycosyl thiocyanates as glycosyl donors and trityl protected glycosyl acceptors. Thiocyanate donor **90** and C-6 tritylated acceptor **91** gave dimer **92** as the α-anomer (Scheme 25). This reaction is initiated by the nitrogen atom of the isocyanate reacting with the trityl cation with simultaneous nucleophilic attack of the C-6 oxygen atom of the trityl protected acceptor at the anomeric position in an S_N2 type fashion resulting in the synthesis of α-glycoside **92**.



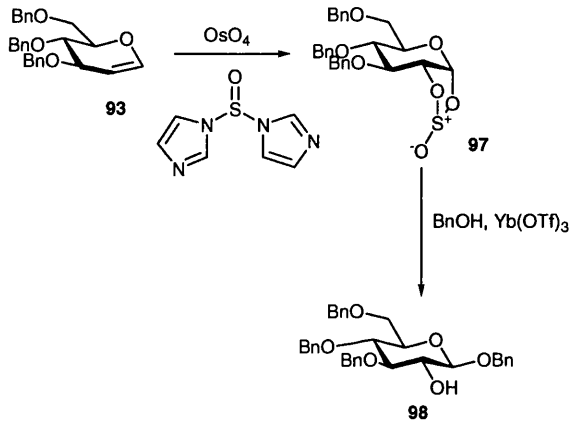
Scheme 25: *Thiocyanates and inversion of configuration*

Danishefsky and co-workers[64-67] have shown that the choice of protecting group can affect the type of reaction mechanism observed, along with preventing *in-situ* anomerisation. In their study of the reaction of 1,2-*cis* epoxides **94** obtained by epoxidation of glucal **93** with dimethyldioxirane (DMDO), with glycosyl acceptor **95** promoted by $ZnCl_2$, selective entry to the 1,2-*trans*-glycoside **96** (Scheme 26) was achieved. Conversely, van Boom and co workers[68] demonstrated that the $ZnCl_2$ mediated glycosylation of 1,2 *cis*-epoxides, produced from a glycal, resulted in mixtures of anomers. In this case the reaction appears to proceed *via* a S_N1 mechanism (Scheme 26).



Scheme 26: *Inversion using glycals*

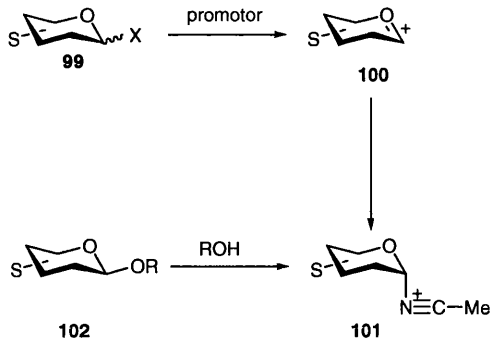
Kissing and co-workers have used 1,2-cyclic sulfites as epoxide analogues because of their relative ease of preparation and decreasing lability in comparison with the corresponding epoxides. In their strategy, osmylation of glucal **93** proceeded with high diastereofacial selectivity (19:1) to give the corresponding 1,2-diol in high yield (91%), which when treated with thionyl imidazole which gave exclusively the 1,2-*cis* sulfite **97**. Subsequent activation with lanthanide (III) triflate in the presence of benzyl alcohol resulted in the formation of predominantly the 1,2-*trans*-glycoside **98** (10:1) (Scheme 27).



Scheme 27: *Sulfite mediated inversion*

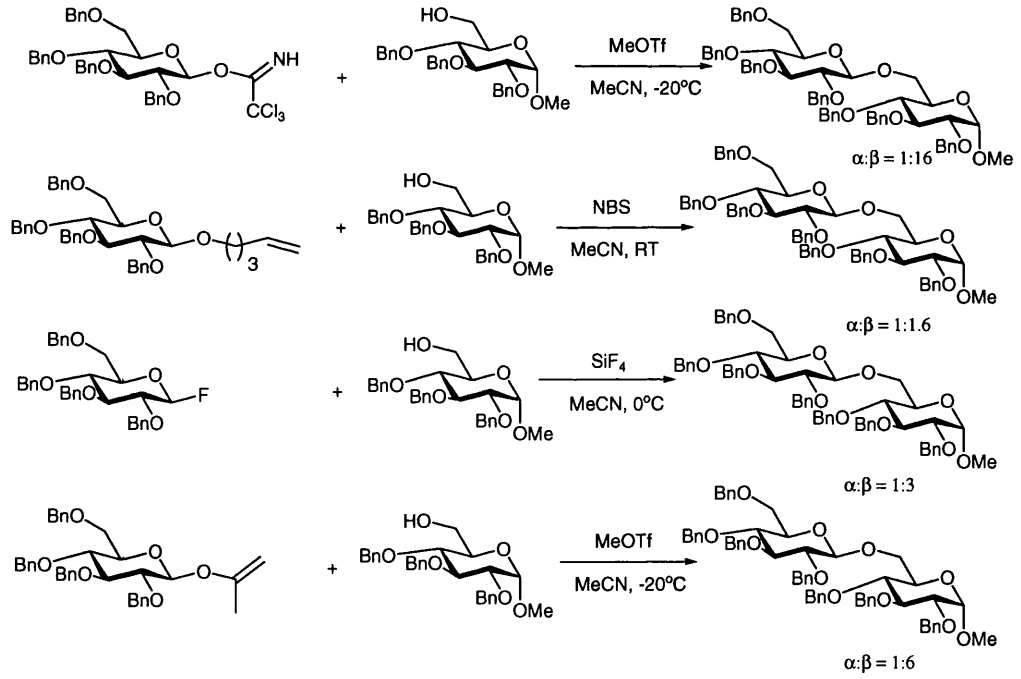
1.7 Solvent participation

The use of a participating solvent has allowed for an additional element of control over the anomeric outcome of glycosylation reactions. Several groups have employed acetonitrile as the reaction solvent since it results in the formation of an equatorial glycosidic bond.[69-71] A number of groups have proposed that an α-nitrillium ion **101** is formed under a S_N1 type process and this then undergoes a S_N2 reaction with inversion to give the corresponding β-glycoside **102** (Scheme 28). This mechanism is prevented if a C-2 participating functionality is present, so careful choice of protecting group is also essential in this process.



Scheme 28: *Solvent Participation*

The feasibility of this process has been investigated by examination of a range of donor types e.g. trichloroacetimidates (**7**), fluorides (**6**), phosphates (**9**), pentenyl (**10**), and thioglycosides (**8**). Scheme 29 shows that the highest β-selectivities are seen at low reaction temperatures. It has also been shown that mannosides give poor selectivities.



Scheme 29: *Examples of solvent participating glycosylations*

1.8 Chemoselective glycosylations[72-75]

For a given glycosylation the reaction mechanism may exhibit a low or high degree of S_N1 character. Nevertheless the rate determining step for the reaction is still dependant upon the development of positive charge in the transition state. As a

result, the electronic effects of the ring substituents and that of the anomeric centre of a particular glycosyl donor may significantly affect the reactivity and stereoselectivity of any given glycosylation.

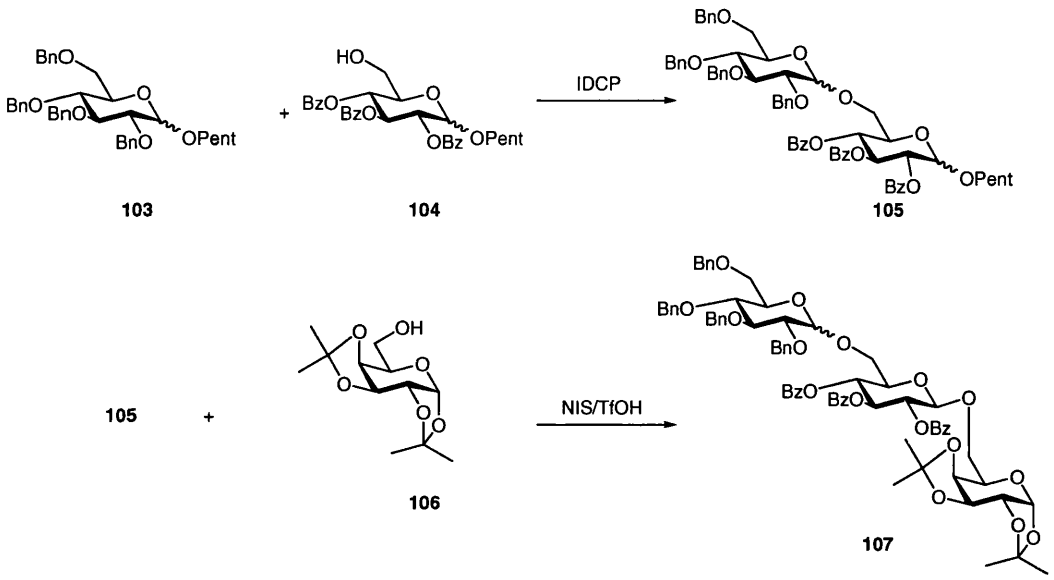
This general chemoselective method has been further expanded to include ideas based upon chemoselective glycosylations. Numerous strategies can be described: active/latent (switching on or off a particular donor by manipulation of the leaving group), side tracked (reversible deactivation of a glycosyl donor before conversion back to its active form), one-pot (the use of differing levels of reactivity in order to tune sequentially controlled glycosylations with different donors one after another), and orthogonal glycosylations (the use of donors under mutually exclusive conditions). These tactics will be considered in the following pages.

1.8.1 Armed/disarmed glycosylations

It has been shown that the use of electron donating ether protecting groups tends to stabilize the oxonium ion intermediate, resulting in an increase in the rate of the reaction. [29-31,76] Donors possessing electron donating protecting groups that can enhance the reactivity of a glycosylation are termed 'armed'. Conversely, donors bearing electron withdrawing groups such as esters as electron withdrawing protecting groups are termed 'disarmed'.

Fraiser-Reid and co-workers were involved in pioneering work in this area [29,77] They coupled C-2 protected benzyl ether pentenyl glycoside **103** to C-2 protected benzoate ester pentenyl glycoside **104** demonstrating chemoselective glycosylation using the same anomeric composition in both the donor and acceptor. Activation of the armed donor with iodonium dicollidine perchlorate (IDCP) gave dimer **105** as an anomeric mixture in 62% yield. Further activation was then possible under more powerful

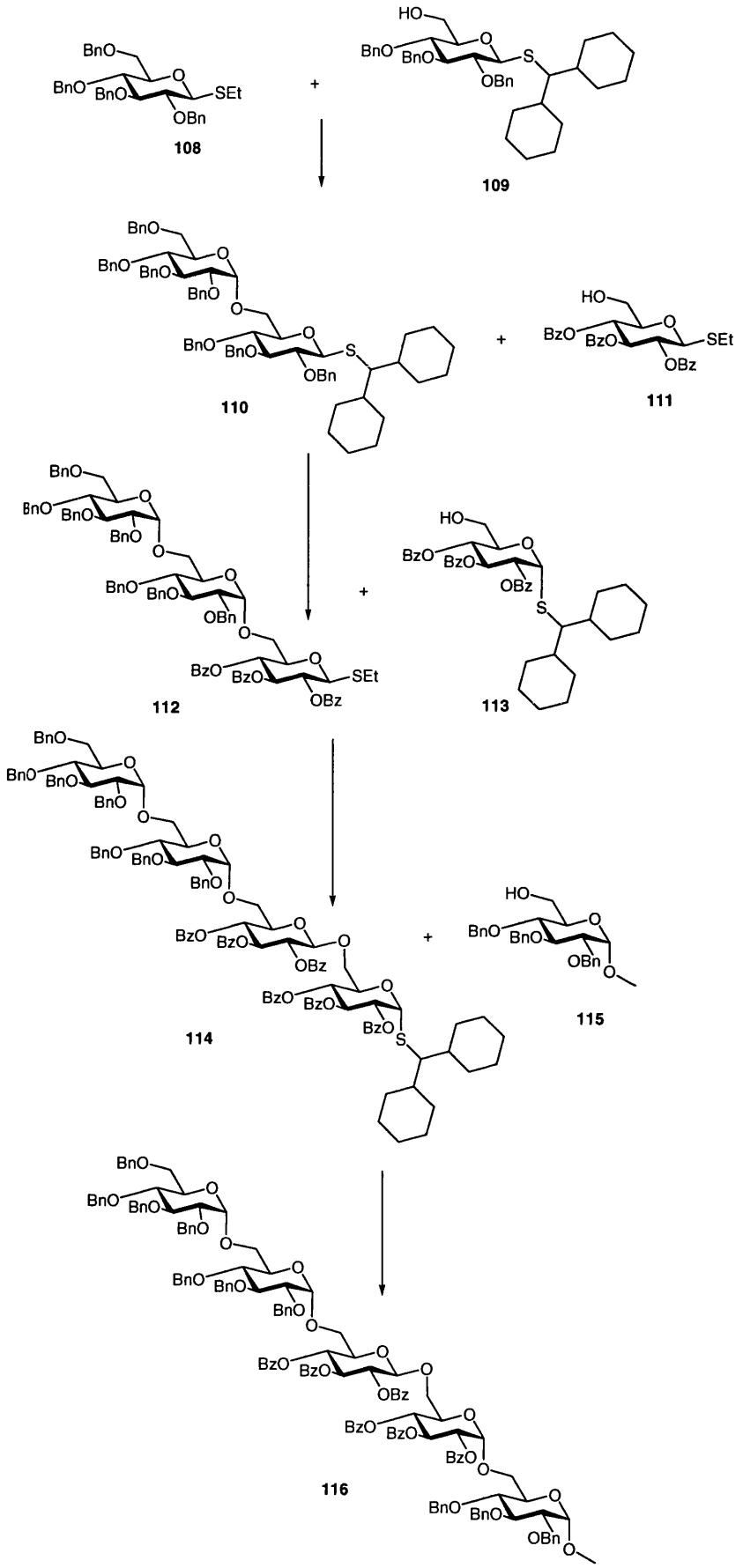
activation conditions of *N*-iodosuccinimide/catalytic triflic acid (NIS/TfOH) in the presence of acceptor **106** to yield trisaccharide **107** (60%) (Scheme 30).



Scheme 30: *Chemoselective pentenyl glycosides*

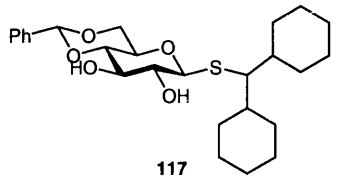
1.8.2 Effects of the leaving group (active/latent & side tracked methodologies)

The nature of the leaving group can be modified to control reactivity in glycosylation reactions. For example a reactive thioglycoside donor can react with a less reactive thioglycoside acceptor which can also act as a glycosyl donor if more reactive activation conditions are employed. Boons and co workers have demonstrated the use of armed and disarmed dicyclohexylmethyl thioglycosides **109** and **113** respectively (Scheme 31) as donors.[78] The steric bulk of this thioether results in deactivation of the perbenzylated thioglycoside **108** to a (semi-disarmed) reactivity level between perbenzylated ethyl thioglycoside **108** and peracetyl ethyl thioglycoside **112**. In addition to this level of selective activation, the α and β anomers of the dicyclohexylmethyl thioglycoside also showed chemoselective activation. Employment of the dicyclohexylmethyl thioglycoside **110** as an acceptor then donor allowed for the production of a phytoalexin elicitor β-hexaglucoside along with pentasaccharide **116** (Scheme 31).[79]



Scheme 31: *Chemoselective thioglycosides*

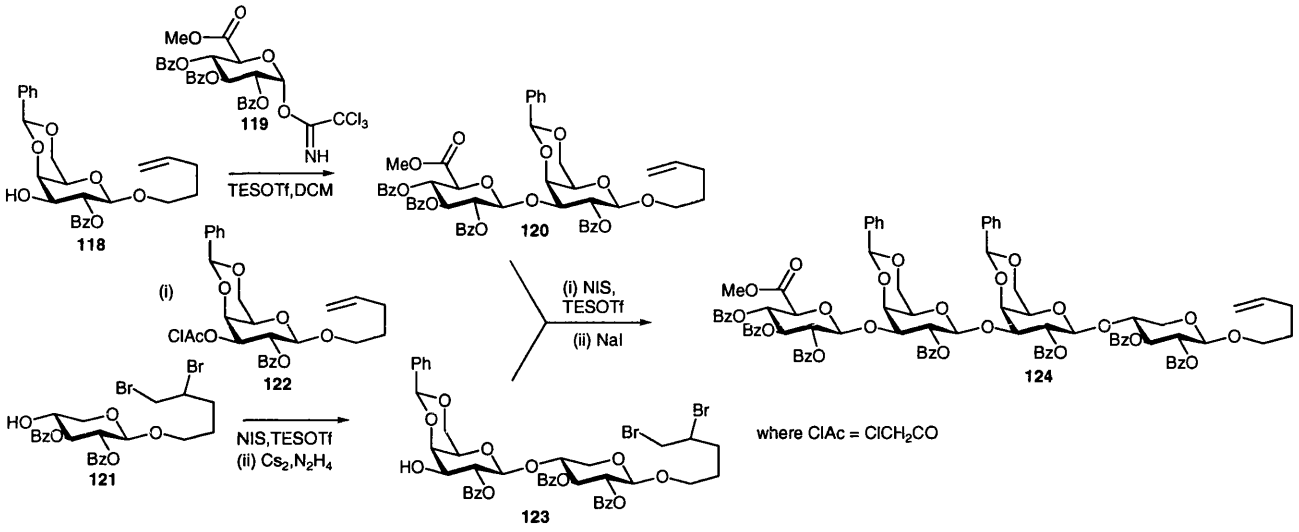
Fraiser-Reid and Allen have prepared tetrasaccharide **124** from the protein to glycan linkage region of proteoglycans.[80] The key common intermediate used was that of benzylidene **117** (Figure 14) which was prepared from the corresponding pentenyl orthoester.



117

Figure 14: *Bis-cyclohexylthioglycoside 117*

The use of acylated donors results in the formation of orthoesters from the starting thioglycoside, although benzoate ester **118** demonstrates significant reactivity whilst retaining the desired C-2 directing capabilities allowing β-galactoside synthesis. In their procedure Fraiser-Reid and Allen employed orthogonal glycosylation of **118** with trichloroacetimidate donor **119** to give the new donor system β-glucuronate galactose based disaccharide. Pentenyl glycosyl donor **122** was then used with acceptor deactivated dibromide acceptor **121** which was termed 'side tracked' due to the deactivation of its pentenyl precursor. Glycosyl acceptor **121** was prepared by bromination of the pentenyl glycoside enabling its use as an acceptor to give disaccharide **123**. This was then returned to its active pentenyl state by iodide induced elimination post tetrasaccharide **124** construction (Scheme 32).

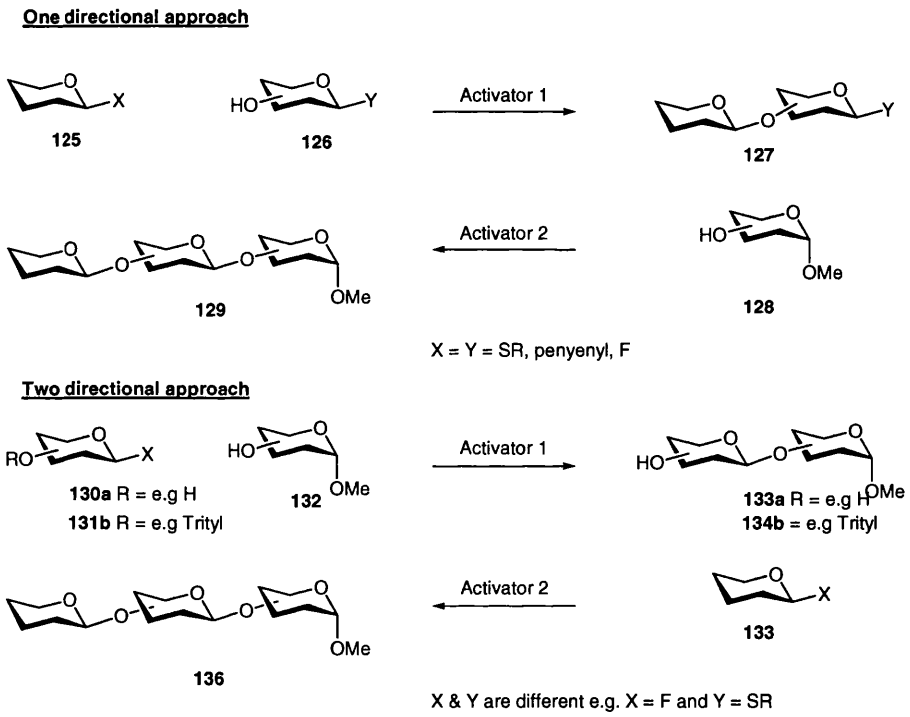


Scheme 32: *Chemoselective tetrasaccharide synthesis*

1.8.2 Chemoselectively exclusive leaving group glycosylations (orthogonal glycosylations)

Efforts over the past 10 years have been directed towards the synthesis of complex oligosaccharides using the minimal number of synthetic steps. Commonly a linear approach has been utilised where both the glycosyl donor and acceptor can possess the same type of anomeric leaving group as seen for glycosyl donor **125** and acceptor **126** (Scheme 33) (e.g. X=Y=SR, F, pentenyl). These systems show different reactivities which are controlled predominantly by the careful selection of protecting groups. Strategies have, however, been employed where different anomeric leaving groups have been used in both the donor and acceptor in a linear strategy. Both of these linear strategies have been used and offer advantages such as limiting the number of protecting group manipulations required during the synthesis of complex oligosaccharides and allowing their use in solid supported methodologies. Neither of these strategies, however, solves the problem of having the glycosyl donor as the growing oligosaccharide in each glycosylation step which can markedly affect the reactivity at each glycosylation step.

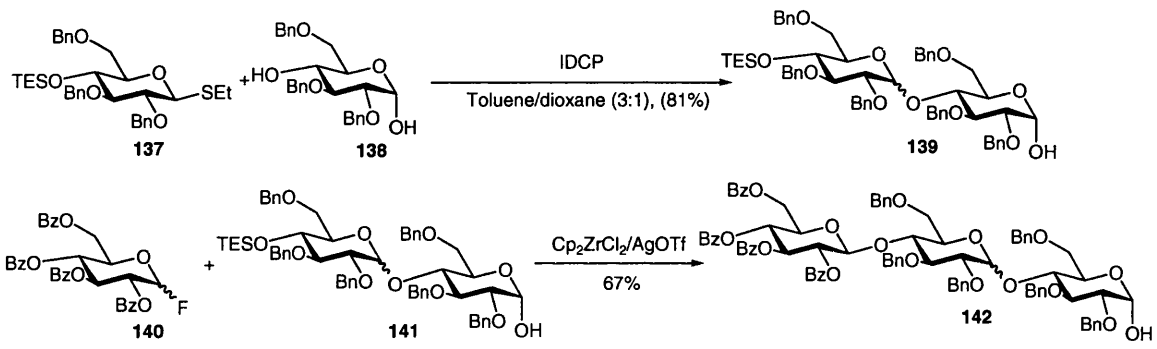
Boons and co workers have developed a two directional glycosylation approach in combination with orthogonal glycosylation methodologies in the production of a range of trisaccharides. This two directional approach uses the partially protected glycosyl donor **130** which is coupled to glycosyl acceptor **132** (Scheme 33). The product **133** then possesses a free hydroxyl group which can be used in further glycosylations. [81,82] Combination of this with previously reported glycosylations (e.g. **137** = **131** Scheme 34) made it possible to construct tri- and tetrasaccharides with minimal protecting group manipulations between glycosylation steps.



Scheme 33: *O*ne directional glycosylation

The requirement for this is that the hydroxyl group of the acceptor is significantly more reactive than that within the donor. This limitation was overcome by the use of tritylated thioglycosides[82]as donors since they can be easily converted into reactive acceptors under specific reaction conditions. [83,84] Moreover, the use of primary and secondary silyl ethers which are initially inert under the first glycosylation conditions are subsequently activated under alternative reaction. For example, the secondary

silyl ether **137** was activated with IDCP in the presence of acceptor **138** to give the disaccharide **139** in 81% yield. Subsequent reaction of **139** now acting as an acceptor with benzoyl protected glycosyl fluoride **140** in the presence of the Cp_2ZrCl_2/AgOTf activator system resulted in the formation of trisaccharide **142** in a respectable 67% yield.

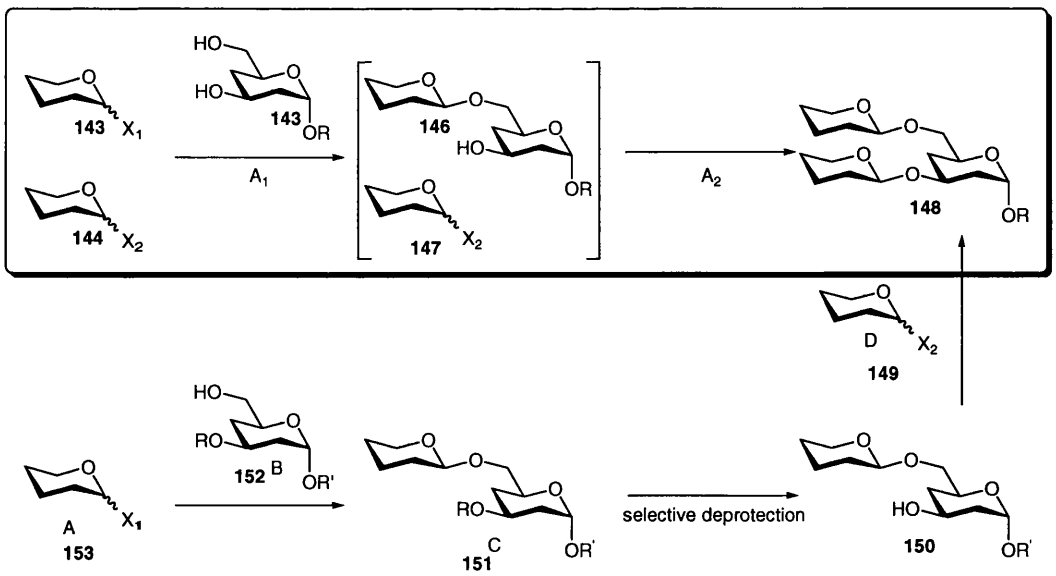


Scheme 34: *Chemoselective silyl ethers*

1.9 One pot multi-step glycosylations

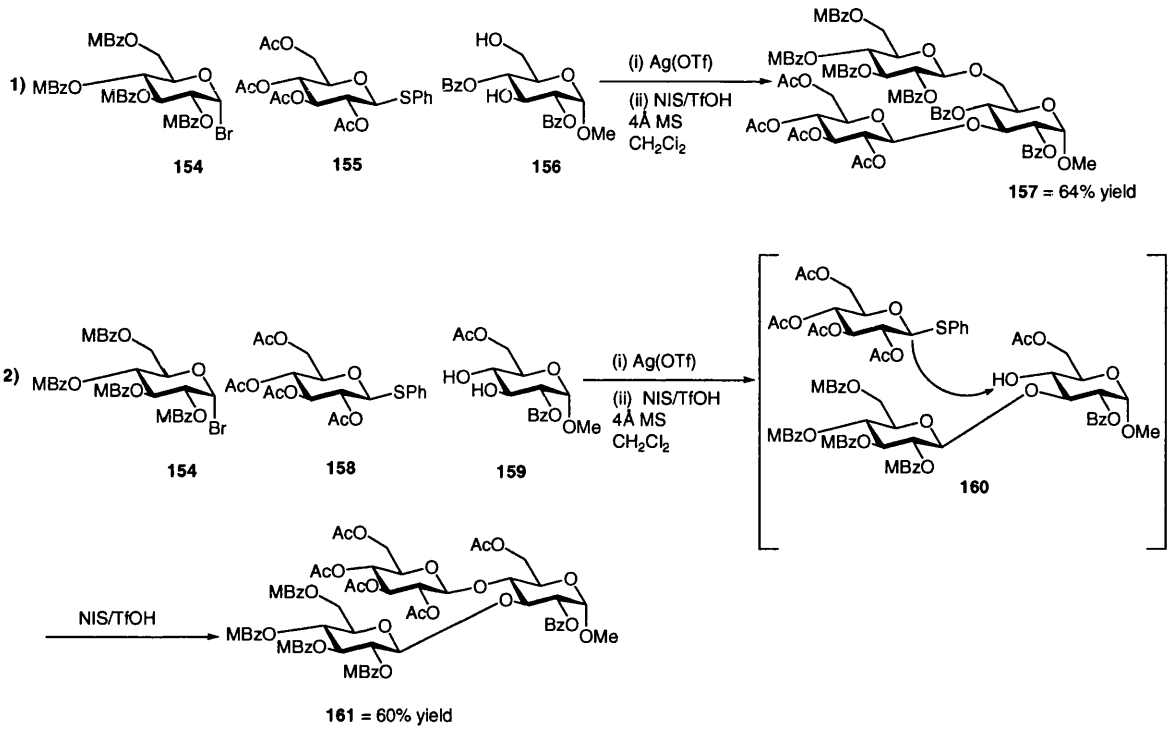
A significant proportion of research in the general area of oligosaccharide synthesis revolves around the use of fully protected glycosyl donors in combination with a suitably deprotected 'free' hydroxyl group. However, there has been significant interest in the use of strategically deprotected donors which can act as their own acceptor in an intra-molecular fashion. Furthermore the use of poly (unprotected) glycosyl acceptors has been well reported with the groups of Kahne,[17] Takashi,[85] Ley [86] and Danishefsky.[87] All have made major contributions to chemoselective/one pot methodologies in terms of linear glycosylations. In comparison the synthesis of branched oligosaccharides has been less well documented although Takashi and co-workers[85,88] have demonstrated an elegant one pot synthesis method for the synthesis of branched oligosaccharides. The requirements for such a process include differences in reactivity between not only the glycosyl donors used and also the acceptor alcohols. Scheme 35 depicts the general strategy involved here. The

expectation was that coupling of glycosyl bromide (X_1 = Br, **143, 144**) with acceptor **145** in the presence of activator A_1 (AgOTf) would result in glycosylation at the more reactive hydroxyl group (C-6) to provide disaccharide acceptor **146** (Scheme 35). Activation of glycosyl donor **147** (X_2 = SPh) would not occur due to stability of this donor to the activation conditions, thus addition of a second activator A_2 (NIS/TFOH) would be envisaged to activate this second donor allowing glycosylation at the less reactive hydroxyl group in a one pot procedure. Classically this differs from previous syntheses of branched oligosaccharides due to the requirement for additional protection/deprotection steps. That is, at the beginning of a synthesis an adequately protected glycosyl donor (A) would be coupled to a suitably protected acceptor (B) giving disaccharide (C). Selective deprotection of disaccharide (C) would then result in the formation of a suitably protected disaccharide acceptor allowing glycosylation to occur with a second glycosyl donor (D) under suitable activating conditions, finally resulting in branched trisaccharide **148**.



Scheme 35: *One pot glycosylations*

In their publication Takahashi and co-workers investigate a series of regioselective coupling combinations with the preparation of 2,6-, 3,6-, 4,6-, and 3,4- linked trisaccharides in good yield (Scheme 36).



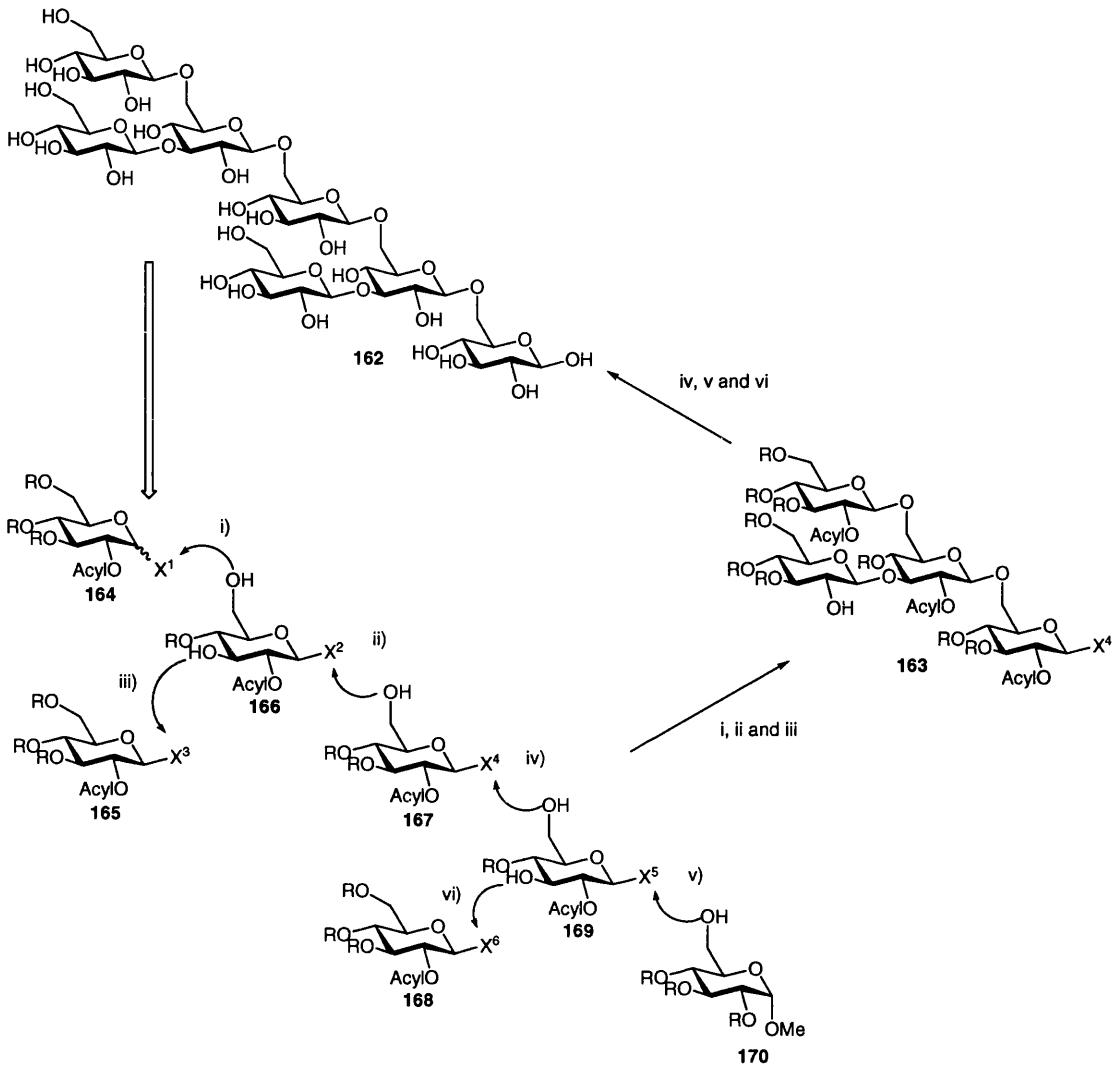
Scheme 36: *Examples of one pot glycosylations*

As can be seen in each case initial coupling of the *p*-methoxybenzoyl protected glycosyl bromide **134** occurs at the more reactive hydroxyl group. In the first case glycosylation takes place from the C-6 hydroxyl group, where there is a choice of primary or secondary alcohol. In example 2 regioselective glycosylation occurs at the more labile C-3 position since equatorial attack is preferred to axial attack (Scheme 36). Subsequent addition of the second promotor system allows glycosylation of the acetate protected phenylthioglycoside resulting in the formation of trisaccharides **157** and **161** all in good yields.

In a further development of their strategy, Takahashi and co-workers have synthesised heptasaccharide **162** which contains four consecutive β-(1,6) linked glucose units for the core 'back bone' along with two β-(1,3) branched glucose units.

Historically the branched structure of **162** has been used as a target for new methodologies for oligosaccharide synthesis.[89-93]

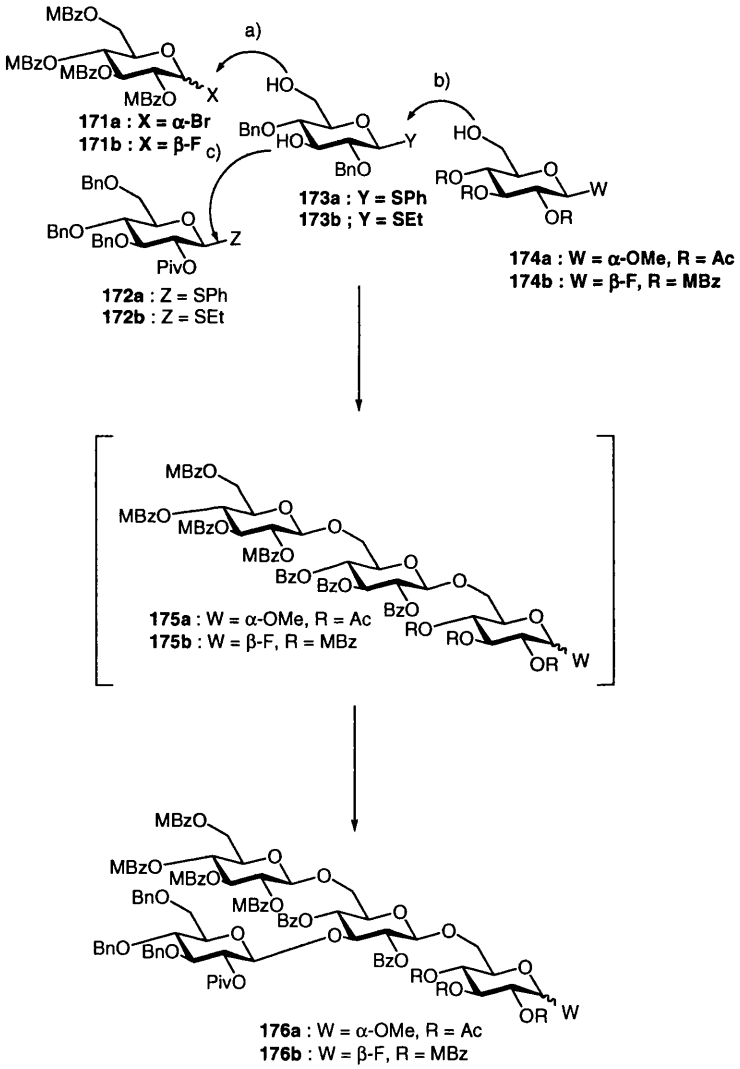
The key strategy outlined in Scheme 37 and requires sequential activation of six glycosyl donors in a reaction sequence which include: (i) regioselective glycosylation of primary alcohol **166** in the presence of a secondary alcohol (ii) glycosylation of acceptor **167** without self condensation (iii) glycosylation of secondary acceptor fragment **166** with glycosyl donor **165** to give the tetrasaccharide **163** (Scheme 38).[81,94-96] This tetrasaccharide can be constructed from only two different donor types as the same donors were used in the third and fourth glycosylation steps in a different strategy to their previously reported strategy for the synthesis of **176.**[97] Thus a successive 'one pot' glycosylation initiated by the synthesis off the tetrasaccharide **175** using three saccharide building blocks **168**, **169** and **170** (iw, v, vi) (Scheme 37) gave a one pot synthesis of heptasaccharide **179** using only the following types of donors: glycosyl bromide **6** (**X** = Br), ethylthioglycoside **8** (**R** = alkyl), glycosyl fluoride **6** (**X** = F) and phenylthioglycoside **8** (**R** = Ph)) activated by the following promoter systems respectively AgOTf, [89] MeOTf,[98,99)] $HfCp_2Cl_2$/AgOTf [100]and DMTST.[16]



Scheme 37: *Retrosynthetic analysis for one pot heptasaccharide synthesis*

The first part of the procedure is the one-pot synthesis of tetraglycosyl fluoride **176b** using the four building blocks **171a**, **172b**, **173b**, and **174b**. The synthetic sequence but not the reaction mechanism is shown in the first part of Scheme 38. Glycosylation of thioglycoside **173b** with glycosyl bromide **171a** (1.1 equiv) in the presence of AgOTf was then followed by coupling of glycosyl acceptor **174b** in the presence of excess MeOTf to provide trisaccharide donor **175b**. Activation of thioglycoside **172b** (1.8 equiv) with the residual MeOTf gave branched tetrasaccharide **176b** in a 48% yield. The presence of excess activator in the second glycosylation step meant that no activator needed to be added for the third

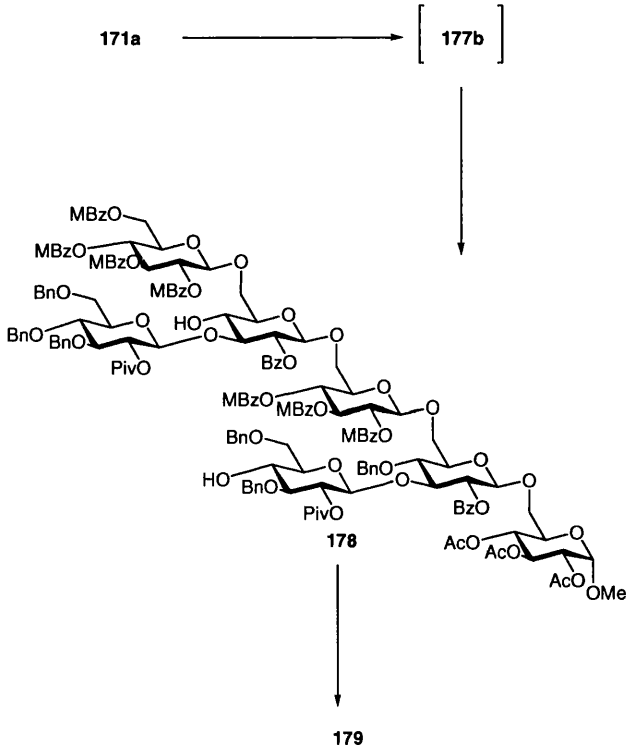
glycosylation step. The coupling **173a**, **174a** and **172a** was then investigated with **171b** instead of **176b**. It was found that the coupling of **171b** with thioglycoside **172a** (1 equiv) with glycosyl fluoride **171b** (1.1 equiv) and acceptor **174a** (1.1 equiv) was achieved using $HfCp_2Cl_2$/AgOTf as the activator and excess amounts of DMTST. Successive addition of thioglycoside **173a** (3 equiv) resulted in the formation of tetrasaccharide **176a** in a respectable 53% yield.



[a] reagents and conditions. Reaction sequence for **176b**: (a) **171a**, **173b**, AgOTf, CH_2Cl_2, MS4Å, -40°C; (b) **174b**, MeOTf, CH_2Cl_2, rt; (c) 13b, CH_2Cl_2, 48% yield based on 11b.
for **176a**: (a) **171b**, **173a**, $ZrCp_2Cl_2$, AgOTf, MS4Å, CH_2Cl_2, 0°C; (b) **174a**, DMTST, CH_2Cl_2, 0°C; (c) **172a**, CH_2Cl_2, 0°C, 53% yield based on **171a**.

Scheme 38: *One pot glycosylations*

Subsequently the synthesis of the heptasaccharide **179** was attempted (Scheme 39). Initially **178b** was synthesised as described above and then sequential addition of thioglycoside **173a** (I equiv) with $HfCp_2Cl_2$/AgOTf, acceptor **174a** (1.1 equiv) with an excess of DMTST and thioglycoside **172a** (6 equiv) gave protected heptasaccharide **178** in 24% yield based on **173a**. Deprotection of the benzyl ethers $Pd(OH)_2$ under an atmosphere of H_2 and the esters by NaOMe in $MeOH/H_2O$ gave **179** in a 52% yield from **178**.



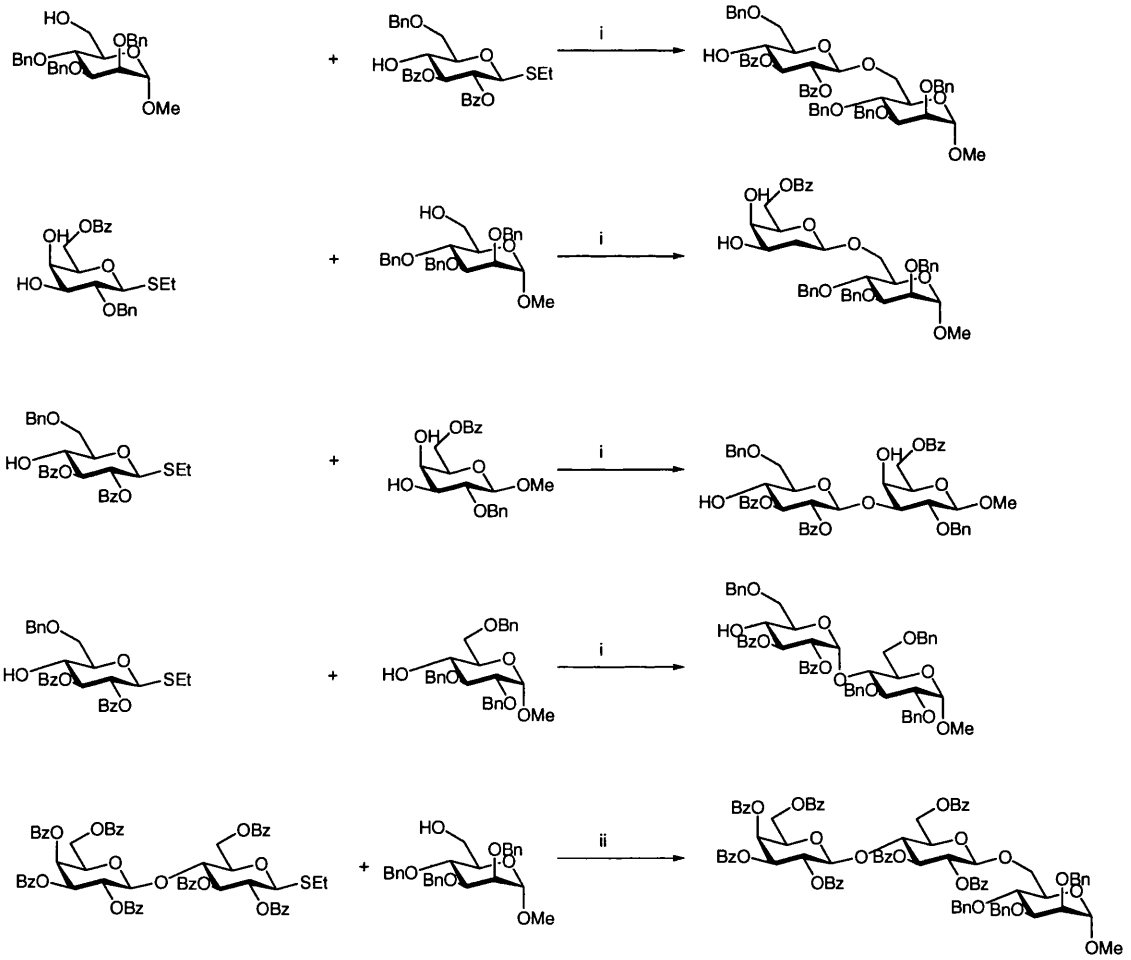
[a]Reagents and conditions: (a) (i) **171a** (1.16 equiv), **173b** (1.10 equiv), AgOTf (2.00 equiv), CH_2Cl_2, MS-4Å, -20 °C, (ii) **174b**, (1.10 equiv), MeOTf (10 equiv), CH_2Cl_2, rt, (iii) **172b** (1.80 equiv), CH_2Cl_2, rt, (iv) **171a** (1.00 equiv), $HfCp_2Cl_2$/AgOTf (2.00 equiv/ 4.00 equiv), CH_2Cl_2, 0°C, (v) **174a** (1.25 equiv), DMTST (12.00 equiv), CH_2Cl_2, 0°C, (vi) **172a** (6.00 equiv) CH_2Cl_2, 0°C, 24% based on **171a**; (b) H_2, $Pd(OH)_2$, $MeOH-H_2O$, 8 h: (c) NaOMe, $MeOH-H_2O$, 12 h, 52% based on **178**.

Scheme 39: *Heptasaccharide synthesis*

1.10 Regioselective glycosylations[101-108]

In the majority of glycosylation procedures, the glycosyl acceptor contains only one 'free' hydroxyl functionality. There are, however, procedures that utilise the differing reaction properties of one or more hydroxyl groups which are unprotected.

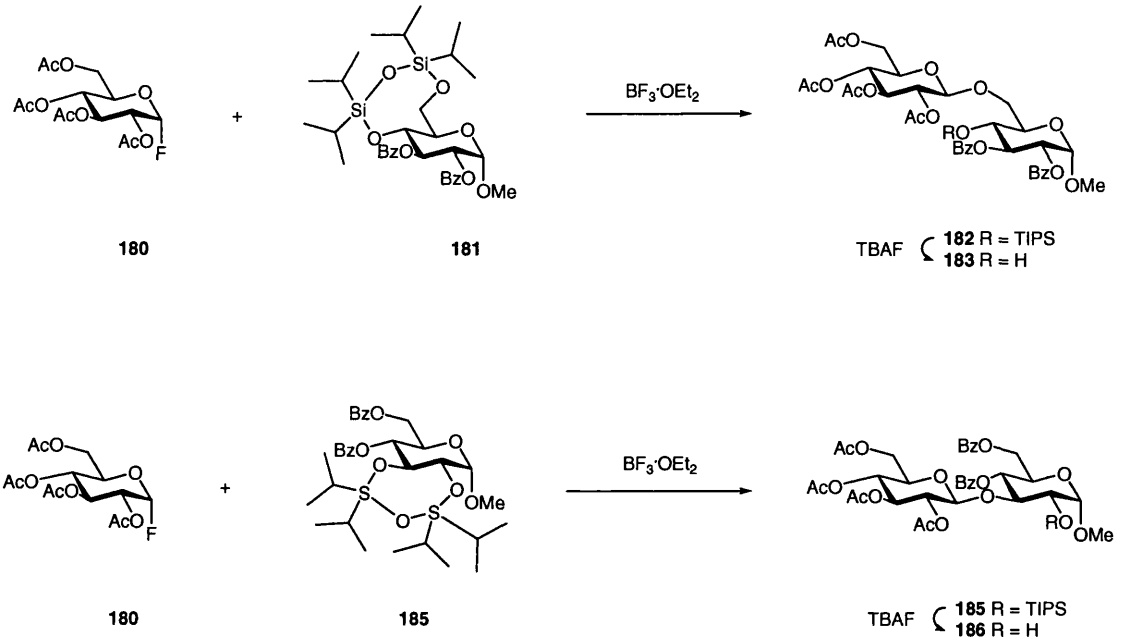
The result is a regioselective glycosylation. An excellent example has been described, which shows this differing reactivity between hydroxyl groups and allowing chemo- and regioselective glycosylation.[96] In their strategy Boons and co-workers utilised the reactivity: primary hydroxyl > equatorial secondary hydroxyl > axial secondary hydroxyl and hydroxyl in ether protected sugars > hydroxyl in ester protected sugars allowing impressively regioselective glycosylation of 3-OH galactose over 4-OH and the use of thioglycosides as donors with free hydroxyl groups (Scheme 40).



Scheme 40: *Regioselective glycosylations*

In another example Ziegler and co-workers demonstrated a regioselective glycosylation using O-3 and O-4 protected silyl ethers. In their strategy 1,1,3,3-

tetraisopropyldisiloxane-1,3-diyl 9 (TIPS) protected glycosides are used as protected acceptors in a regioselective glycosylated strategy using glycosyl fluorides as donors with $BF_3{\cdot}OEt_2$ as the promoter (Scheme 41). In their example, treatment of **181** with glucopyranosylfluoride **180** in the presence of a catalytic amount of $BF_3{\cdot}OEt_2$ in dichloromethane resulted in glycosylation exclusively at the C-6 position to give β-linked disaccharide **182** in 71% yield. It was also observed in this reaction that a small amount of the partially hydrolysed monomer was isolated. From this it was inferred that the $BF_3{\cdot}OEt_2$ is not only acting as the activator for this system but also partially hydrolyses the silyl diether. Removal of the C-4 silyl group was achieved by the addition of tetrabutyl ammonium fluoride to give **183** (Scheme 41). When the 2,3-di-*O*-TIPS-protected methyl glycoside **184** employed was treated with fluoride **180** in the presence of $BF_3{\cdot}OEt_2$ Laminaribioside **185** was formed exclusively. When the 4,6-benyylidene-α-D-glycopyranoside protected variant was coupled to 2,3,4,6-tetra-*O*-acetyl-α-D-glycopyranosyl bromide only the C-2 glycosylated product was observed. This reversal of regioselectivity can be explained by the fact that the C-2 position of **184** is very sterically crowded, forcing the glycoslation to proceed at the C-3 position.

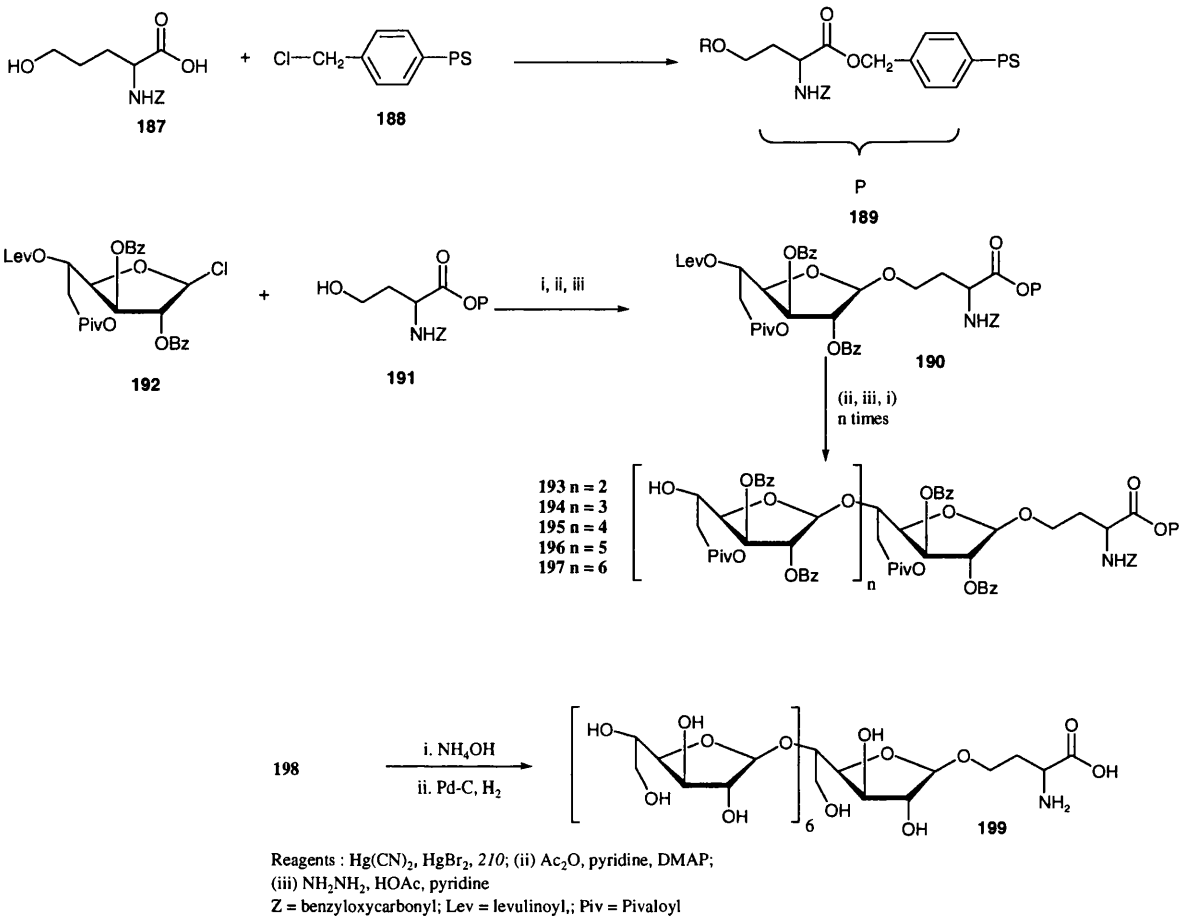


Scheme 41: *Regioselective glycosylations with silyl ethers*

1.11 Solid support in the synthesis of oligosaccharides[109-120]

The research interests of several large research groups in the area of solid supported oligosaccharide synthesis was inspired by the progress made in the synthesis of peptide and oligonucleotide synthesis carried out in the early 1970's.[121-129] Initially, the major problems with this methodology stemmed from the fact that at that time there were limitations arising form the lack of highly successful methods for glycosidic bond synthesis. However, in the late eighty's van Boom and co workers reported the solid phase synthesis of a D-galactofuranosyl heptamer.[130] The synthesis is outlined in Scheme 42. The trityl protected homo serine **187** was linked to the Merrifield polymer chloromethyl polystyrene (PS = polystyrene) **188** to give functionalised polystyrene **189** by the addition of caesium carbonate. Subsequent removal of the trityl protecting group by acid hydrolysis gave functionalized polymer acceptor **191** which was observed to have a loading capacity of polymer of 0.5 mmol g^{-1} resin. Coupling of **191** with the chloride **190** under Koenigs Knorr conditions afforded homoserine glycoside **192**. In their synthesis it was observed that the coupling reaction did not proceed to completion as a result of which acetyl protection of uncapped hydroxyl functionality by reaction with acetic anhydride in the presence of pyridine and *N, N*- dimethylaminopyridine (DMAP) was needed. Synthesis of the resultant heptasaccharide was performed firstly by removal of the levulinoyl (Lev) protecting group of **192** by treatment with hydrazine-pyridine-acetic acid mixture. The resultant alcohol was coupled with chloride **190**, unreacted hydroxyls were then capped again by acetylation. This procedure was then repeated another five times (n = 6) and then cleaved from the serine linker by basic hydrolysis. This process also has the benefit of cleaving both the benzoyl and pivaloyl (piv) protecting groups.

The final stage in their synthesis was the cleavage of the benzoloxycarbonyl group (Z) by hydrogenolysis over Pd-C to give **198** in an overall 23% yield (Scheme 42).



Scheme 42: *Polymer supported oligosaccharide synthesis*

Since this publication the development of polymer supported methods of oligosaccharide synthesis has led to the publication of a number of significant articles, including the recent publication of a flourous based methodology by the group of Inazu and co-workers.[110] In their strategy, Inazu and co-workers use the novel flourous protecting group hexakisfluorous chain type butanoyl (Hfp-OH) (Figure 15), which possesses six flourous chains which are used to make full benefit of the advantage of flourous solvents being both insoluble in aqueous and common organic media allowing a three tier separation potential between the three types of solvent systems.

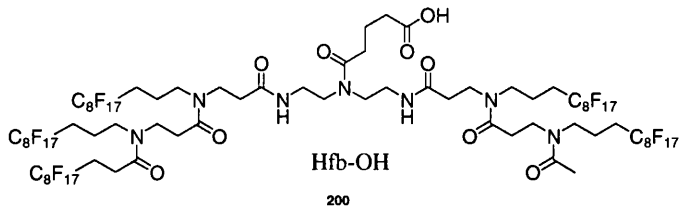
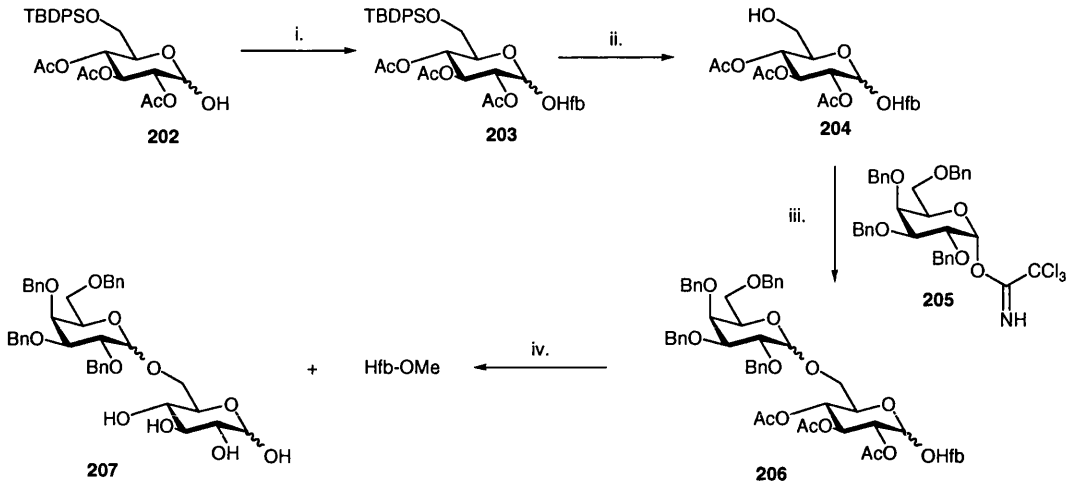


Figure 15: *Hexakisfluorous linker*

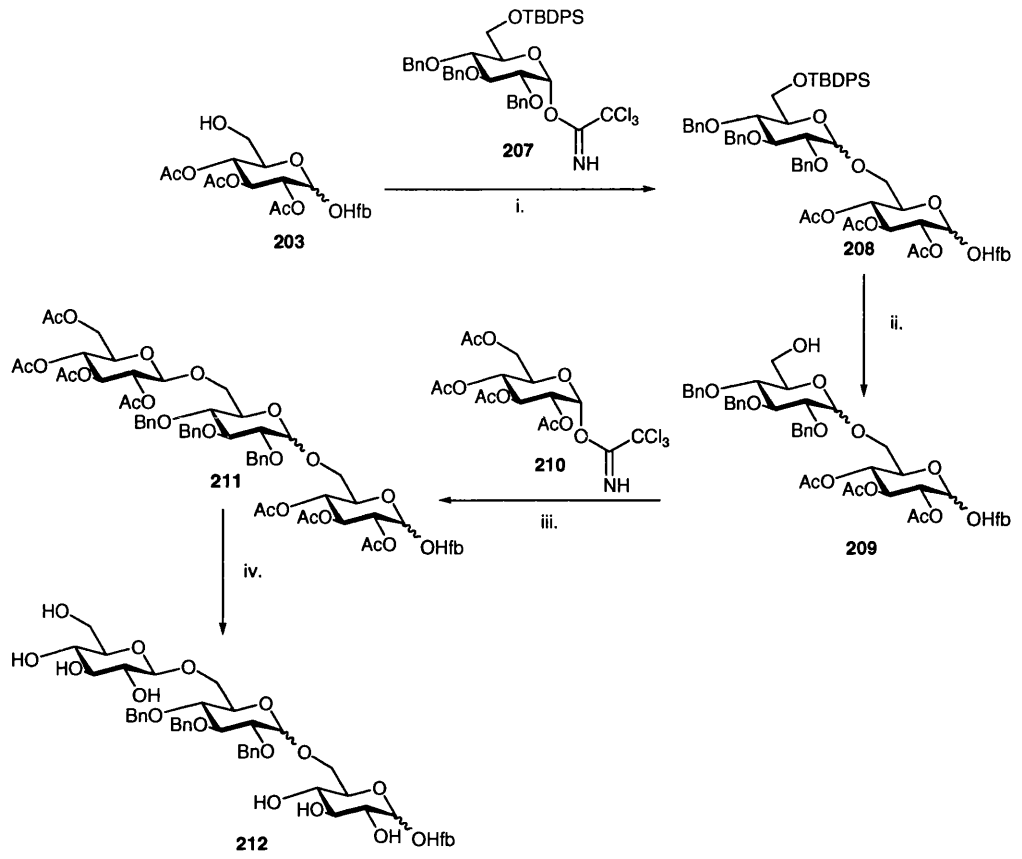
This methodology was used to synthesise di- and tri- saccharides **206** and **212**. Attachment of the fluorous support to the glycosyl donor **202** with the addition of PyBOP and DMAP gave fluorous compounds **202** in the case of the disaccharide protocol. The TBDPS group was removed by the addition of HF-pyridine in THF to give flourous based acceptor **203**. Disaccharide synthesis was achieved by reaction with nine equivalents of glycosyl donor **204** in the presence of TMSOTf in $Et_2O/EtOC_4F_9$, intermediates **204**, **205**, and **206** were separated by partitioning with flourous solvent FC-72. This process negates the requirement for column chromatography, which is an obvious advantage because this can be one of the major stumbling blocks in the synthesis of oligosaccharides. Removal of the Hfb protecting group was achieved by the addition of NaOMe in $MeOH/EtOC_4F_9$ to give crude **206** and Hfb-OMe which was separated by partitioning between MeOH and FC-72, and purified by a single chromatographic step to yield disaccharide **206** (Scheme 43) in a 67% yield from **202** in an impressive 4 steps. Regeneration of Hfb-OH **200** was achieved by the addition of aqueous NaOH and reused.



Reagents and condotions: i., PyBOP, DMAP, CH_2Cl_2, rt,20 h; ii. HF-pyridine, THF, rt, iii. TMSOTf, 4 Å MS, $EtOC_4F_9$, 0 °C, 20 min; iv. NaOMe, $EtOC_4F_9$, MeOH, rt, 16h, then silica gel chromatography, 67% from **203** Bn = Benzyl, DMAP = 4-dimethylamino pyridine, TBDPS = *tert*-butyldiphenyl silyl, TMSOTf = trimethylsilyl trifluoromethane sulphonate.

Scheme 43: *Fluorous phase disaccharide synthesis*

The generation of trisaccharide **212** was quickly realised (Scheme 44) by the coupling of fluorous acceptor HO-Hfb with donor **202** to give intermediate fluorous glycosyl acceptor **208**. Subsequent removal of the TBDPS group by the addition of HF-pyridine generated acceptor **209**. Glycosylation with donor **207** proceeded under the previous methodology to afforded fluorous disaccharide **208**. A second removal of TBDPS from disaccharide **208** gave fluorous acceptor **209**. Coupling of **209** with donor **210**, gave protected trisaccharide **211,** deprotection and extraction as detailed for the disaccharide synthesis gave trisaccharide **212** in an overall yield of 42% based on **203**.

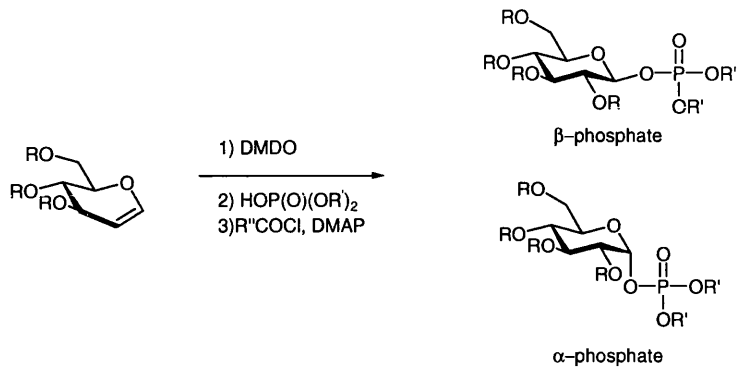


Reagents and conditions: i. TMSOTf 4Å MS, $EtOC_4F_9$, Et_2O, 0°C, 20 min; ii. HF-pyridine, THF, rt, 20h; iii. TMSOTf Å MS, $EtOC_4F_9$, Et_2O, 2 min; iv. NaOMe, $EtOC_4F_9$, MeOH, rt, 14h, then silica-gel chromatography 42% from **207**

Scheme 44: *Fluorous phase trisaccharide synthesis*

Finally in this section it is necessary to mention the outstanding contribution by Seeberger and co-workers towards the automated synthesis of not only linear but even more impressively branched oligosaccharides.[131-135] In their development of an automated system for use in oligosaccharide synthesis they were inspired by the use of glycosyl nucleotide diphosphates in glycosyl transferase reactions. In their studies they focused on the use of glycosyl phosphate triesters (glycosyl phosphates) because of their ease of preparation and effective and versatile use as a glycosylating agent. Glycosyl phosphates are prepared by the reaction of a suitably protected glycal with DMDO generating the corresponding epoxide which then reacts with an appropriate phosphoric acid diester to generate the anomeric phosphate. The anomeric outcome of the reaction can be controlled by the use of an appropriate solvent hence; the use of acetonitrile generates the more reactive β-phosphate whilst the use of a non-

participating solvent results in the generation of the α-phosphate. Subsequent protection of the resulting C-2 alcohol functionality with an acylating agent gives rise to the fully protected glycosyl phosphate (Scheme 45).

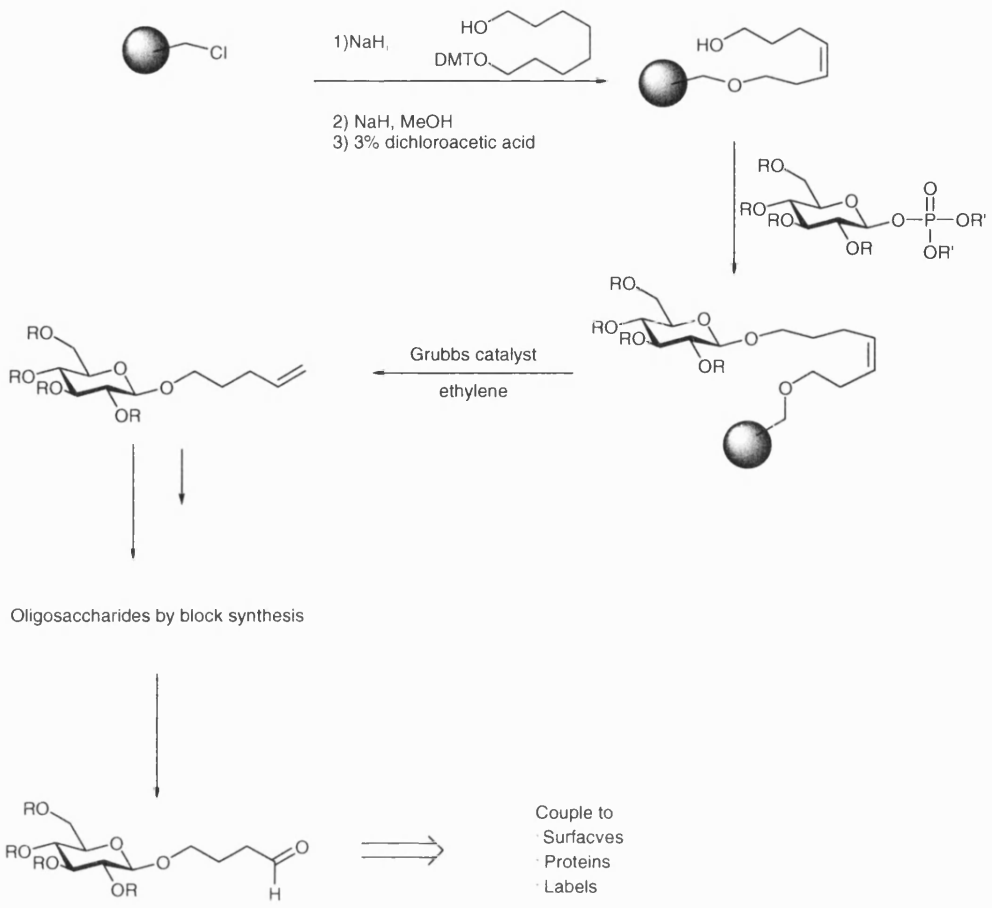


Scheme 45: *Generation of glycosyl phosphates*

Glycosyl phosphates can be activated by the use of TMSOTf or *tert*-butyl dimethyl silyl triflate (TBSOTf). A range of *cis* and *trans* glycosidic linkages were possible when glycosylation studies were performed on *C*-allyl, *C*-alkyl, thio and alcohol acceptors.

The choice of protecting group was then investigated with halobenzyl and 2-azidomethyl benzoate protecting groups, resulting in the production of a range of protecting group patterns for use on polymer support.

The use of an appropriate linker was crucial in linking the first glycoside unit to the polymer support without being reactive to the subsequent glycosylation reactions whilst still being cleavable selectively at an appropriate stage. Seeberger's use of octadiene diol made from cyclooctadiene is easily installed and allows for cleavage of oligosaccharides from solid support by cross-metathesis resulting in the generation of the useful 1-pentenyl moiety which can then be converted to an oligosaccharide by block couplings, the terminal double bond converted to an aldehyde functionality then coupled to either surfaces, proteins or labels (Scheme 46).



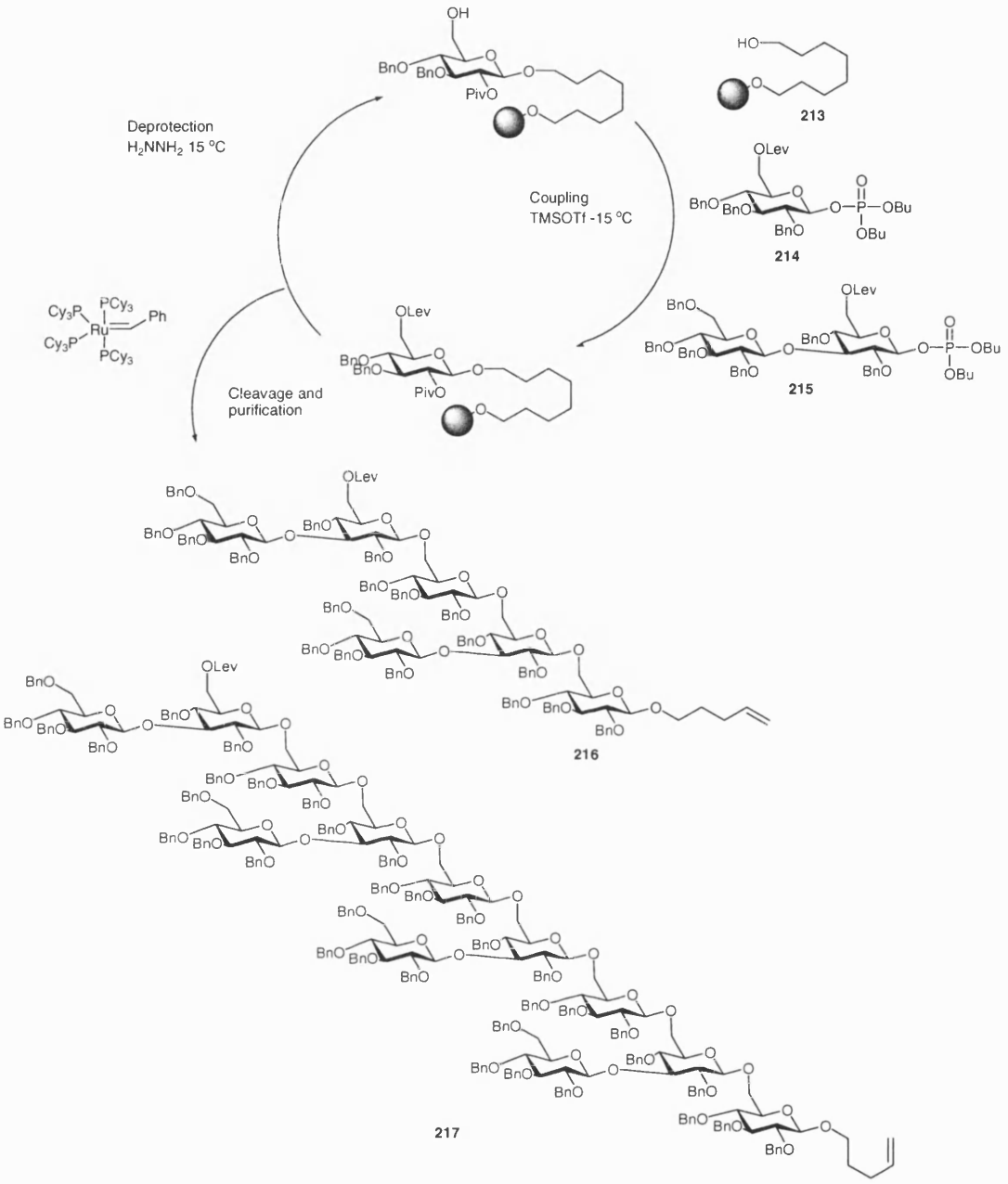
Scheme 46: *Solid phase strategy using glycosyl phosphates*

In their first strategies linear oligosaccharides were attempted generating glycoses and mannoses using glycosyl phosphates and trichloroacetimidates and this was shown to be straight forward. Initial drawbacks were that chain elongation was time consuming with one building block per day being added because of the length of washing and drying steps. As a result of the repetitiveness of the coupling and deprotection steps of the synthesis Seeberger and coworkers saw the possibility for the use of an automated synthesizer which was engineered by the use of an ABI 433 peptide synthesizer and resulted in the ability to generate mg to g amounts of a number of target oligosaccharides. The synthesizer was programmed to perform synthetic sequences as shown in Table 4

Step	Function	Reagent	Time/Min
1	Couple	5 equiv donor & 5 equiv TMSOTf	30
2	Wash	Dichloromethane	6
3	Couple	5 equiv donor & 5 equiv TMSOTf	30
4	Wash	1:9 methanol : dichloromethane	4
5	Wash	Tetrahydrofuran	4
6	Wash	3:2 pyridine : acetic acid	3
7	Deprotection	2× 20 equiv hydrazine (3:2), pyridine : acetic acid	80
8	Wash	3 : 2 pyridine : acetic acid	3
9	Wash	1 : 9 methanol : dichloromethane	4
10	Wash	0.2 M Acetic acid in tetrahydrofuran	4
11	Wash	Tetrahydrofuran	4
12	Wash	Dichloromethane	6

Table 4: *Synthetic sequences for automated oligosaccharide synthesis*

The initial target was the synthesis of the phytoalexin elicitor β-glucan and was their first attempt to address the problem of constructing a branched structure and this was achieved by introducing a disaccharide into a linear assembly sequence. Monnosaccharide **214** and disaccharide **215** were incorporated in an alternating fashion using their coupling cycle (Scheme 47) as a result hexasaccharide **216** was produced in 9h followed by the generation of dodecasaccharide **217** in 16h after purification by HPLC.



Scheme 47: *Automated oligosaccharide synthesis*

Incomplete couplings which result during the process are the most difficult to adresses but this was solved by the use of a capping reagent so called the 'cap' end approach. In addition to capping all unreacted alcohol lost the groups were tagged with the use of azide **218** (A-tag) or flourous based silyl tags **219** (F-tag) Figure 16. The use of the flourous tag would allow for easier purification allowing for separation of deletion sequences from the desired products. Yield optimisation at

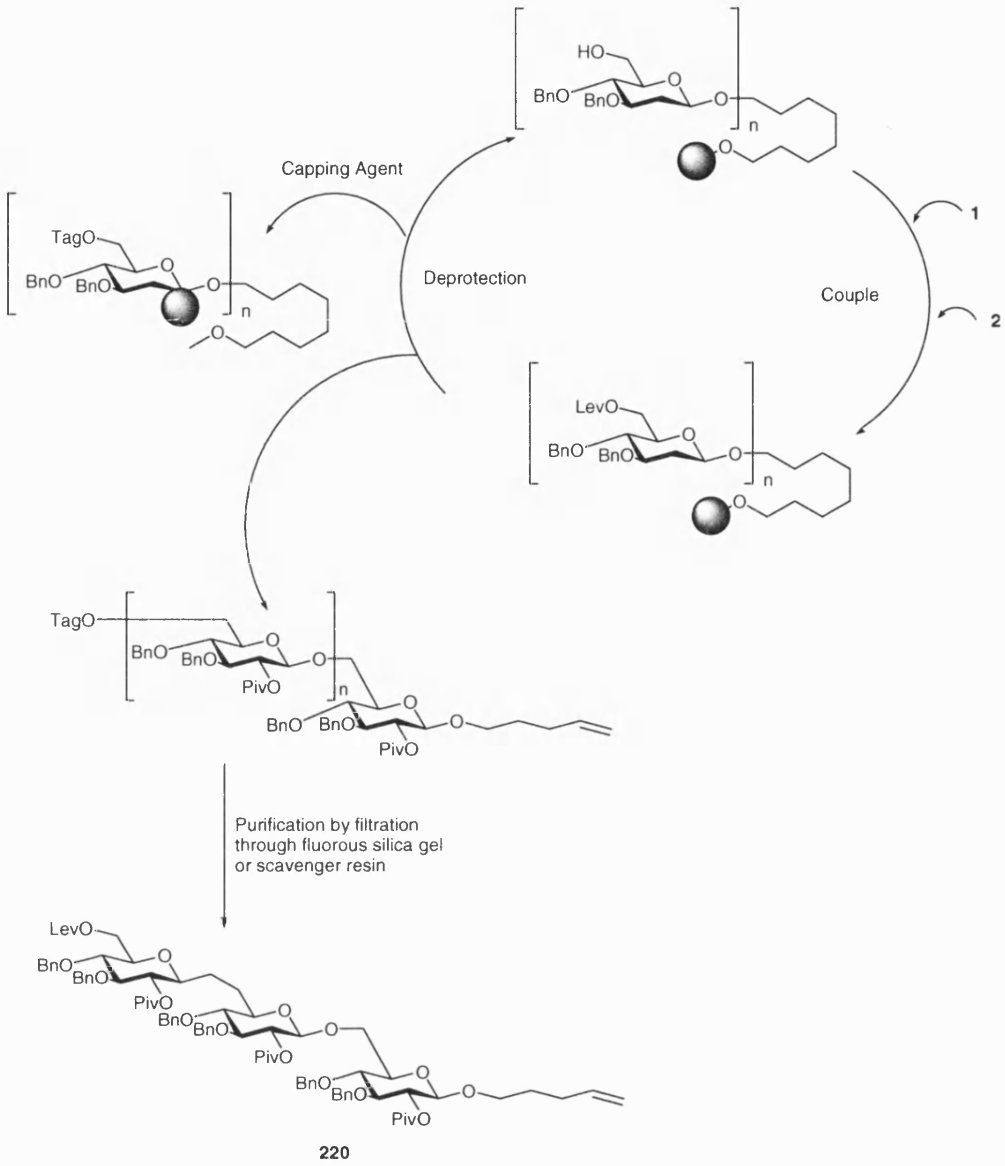
each step was demonstrated by using large excesses of both glycosyl donors used and also reactions were aided by attaching the acceptor rather than the donor to the solid support thus the reactive centre was always the 'monomeric' glycosyl donor a strategy know to improve oligosaccharide synthesis.

218 **219**

A-Tag F-Tag

Figure 16: *Oligosaccharide hydroxyl tags*

This methodology was then utilised in order to synthesise a branch cap tetrasaccharide from the cell surface of protozoan parasite *leishmania* **226** (scheme 48 & 49). The central mannose unit **224** was used and possessed with an orthogonal acetate and levulinate ester protecting group. Attachment to the polymer support preceded removal of the levulinate protecting group then attachment of the glycosyl phosphate **223** and addition of two more mannose trichloroacetimidates gave the desired tetrasaccharide in 9h demonstrating the ability of this system towards the synthesis of branched glycosides. The resultant tetrasaccharide was then conjugated to a protein in order to show a synthetic anti-toxin malaria vaccine figure 17 shows the malaria GPI vaccine candidate **221** Scheme 49 shows the retrosynthetic analysis for the malaria GPI vaccine in a semi automated strategy which allows for the glycosylation of the first 4 monnosaccharide units.



Scheme 48: Synthesis of *Leishmania tetrasaccharide*

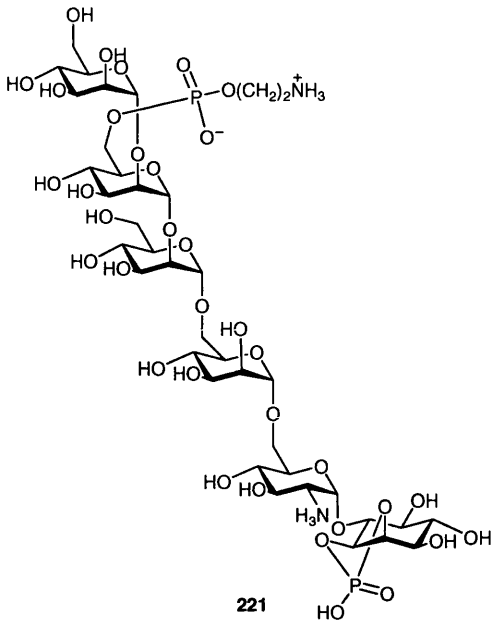
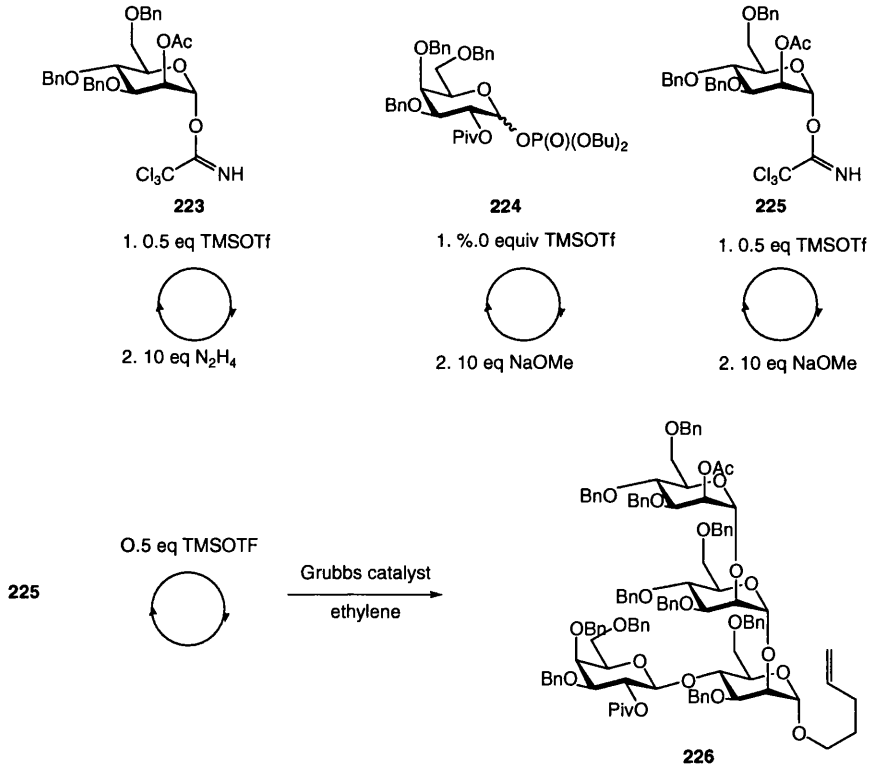


Figure 17: *Maria anti-toxin*



Scheme 49: *Synthesis of Malaria anti-toxin*

In conclusion, this introduction has demonstrated that the degree of technology available to carbohydrate chemists is enormous to say the least, with publications in terms of number being arguably higher than any other single area of organic

chemistry, and is in fact only a fraction of what actually exists. There is a significant number of topic areas not covered in this thesis; for example no mention has been made of the vast number of enzyme based methodologies that have resulted in over 2600 papers being published since 1981,[136-138] also specific methods such as anomeric radical hydrogen abstraction, modifications of the original Koenigs-Knorr coupling methods have also been omitted.[139] All of the above has been heavily reviewed over the years[140-144] and this trend is likely to continue well into the future.

Chapter 2

2 Results and Discussion

2.1 Thioglycosides and their synthetic utility

There are a large number of 1-thioglycosides which occur in nature for example (Figure 18) sinigrin[145](**227**) extracted from the seeds of black mustard and also present in the roots of horseradish. The most relevant example though is the antibacterial agent lincomycin[145](**228**) which is used in the treatment of Gram-positive bacterial infections and organisms which thrive in anaerobic conditions.

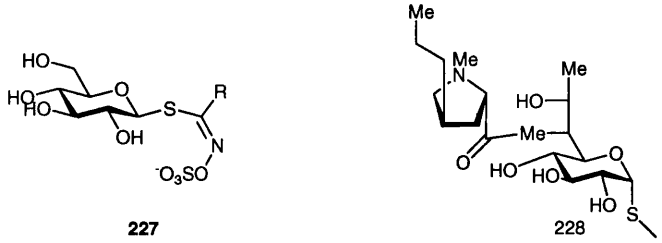
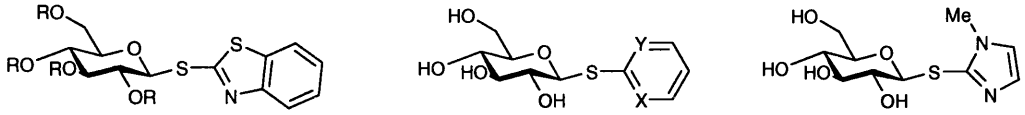


Figure 18: *Examples of naturally occurring thioglycosides*

The synthesis and use of thioglycosides as glycosyl donors has been extremely well documented with over five hundred literature sources quoting their use in terms of new methodologies and donor systems.[140,141,143,144,146,147,148] Thioglycosides have been shown to be selectively activated using a wide range of thiophilic metal activators including mercury(II) salts ($HgSO_4$,[149] $HgCl_2$,[150,151] PhHgOTf,[152] $Hg(OBz)_2$,[153] $Hg(NO_3)_2$, copper(II) triflate[154] and lead (II) perchlorate.[155,156] Glycosylation using these reagents, apart from the use of heavy metals and the obvious toxicity issues thereof, also suffered from low glycosylation yields. Mukaiyama and co-workers[154] have demonstrated the use of benzylthiazolyl thioglycoside **229** (Scheme 50) using Cu(II) triflate as the activator, whilst Hanessian and co-workers have utilized *O*-unprotected glucosyl thio heterocycles **230** and **231** with $Hg(NO_3)_2$ as the activator in order to overcome this weak activation. Hanessian and co-workers were also able to produce Glc(1→6)Gal in good yield although only

modest α/β selectivities were observed. In order to determine the effect of the heteroatom upon activation of the glycosyl donor **230** (X = Y = N) protic activation was carried out whilst comparing the situation where (X = Y= CH_2). The reactions showed the dramatic effect the heteroatom has on the glycosylation as protonation of the heteroatom results in the generation of a better leaving group because of the increased electron withdrawing abilities of the protonated nitrogen.



229 R = Bn **230** **231**

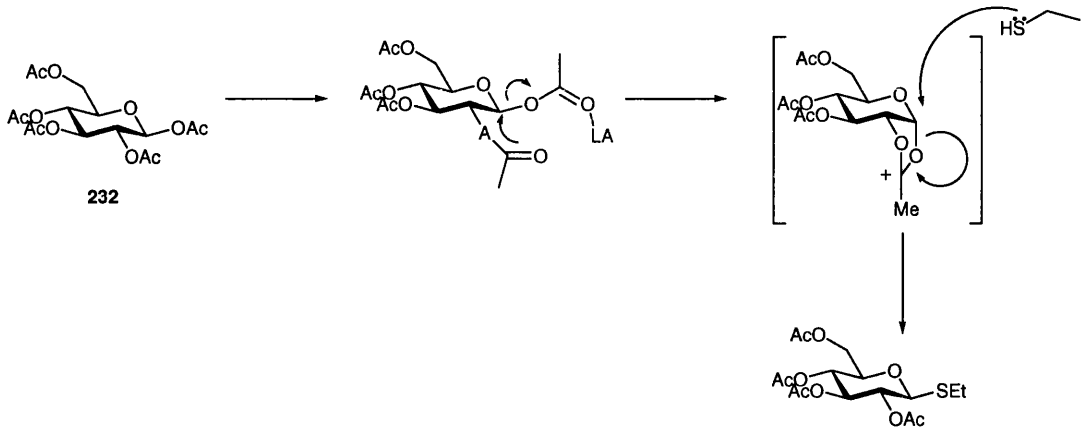
X = N, Y = CH; X = Y = N; X = Y = CH

Scheme 50: *Electronically activated thioglycosides*

Thioglycosides have been shown to be key intermediates in the synthesis of oligosaccharides.[157,158 159, 160] Indeed, their use has covered most of the major categories/methodologies of glycosylation present in the armoury of the modern glycoside chemist which have also been previously discussed in the introduction of this thesis.[161,162] The major advantages in strategies which involve thioglycosides are their: general stability, relative ease of preparation and their ability to be activated under a range of mild conditions.

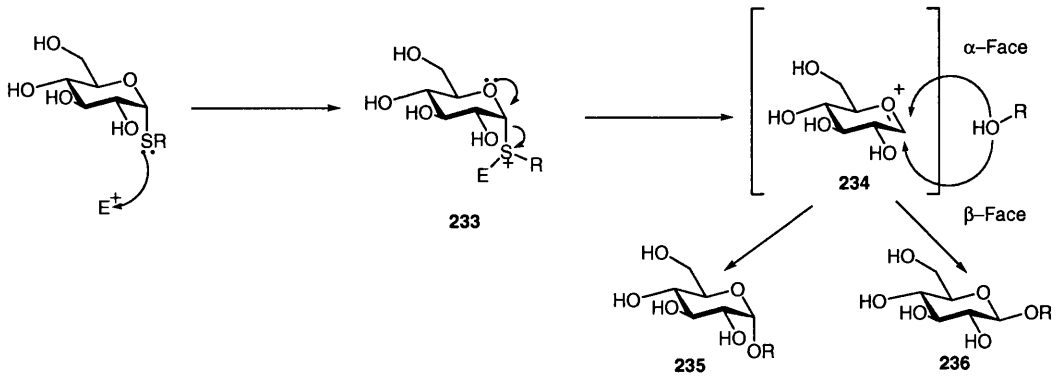
Classically thioglycosides have been synthesized from anomeric acetates upon treatment with a particular thiol in the presence of boron trifluoride diethyletherate (BF_3·OEt) [163] or TMSOTf .[164] Thioglycosides may also be produced by the reaction of an anomeric acetate **232** (Scheme 51) using zinc chloride as the Lewis acidic promoter. Lesser routes towards thioglycosides involve glycosyl donor types such as glycosyl halides and 1-methoxy glycosides. Thioglycosides show stability to aqueous base under normal temperatures, and are hydrolyzed by mineral acids at a

slower rate than that of their oxygen analogues. This increased stability is due to a decrease in the formation of the corresponding conjugate base resulting from the sulfide ($^-$SR) being a weaker base than is an alkoxide ($^-$OR).



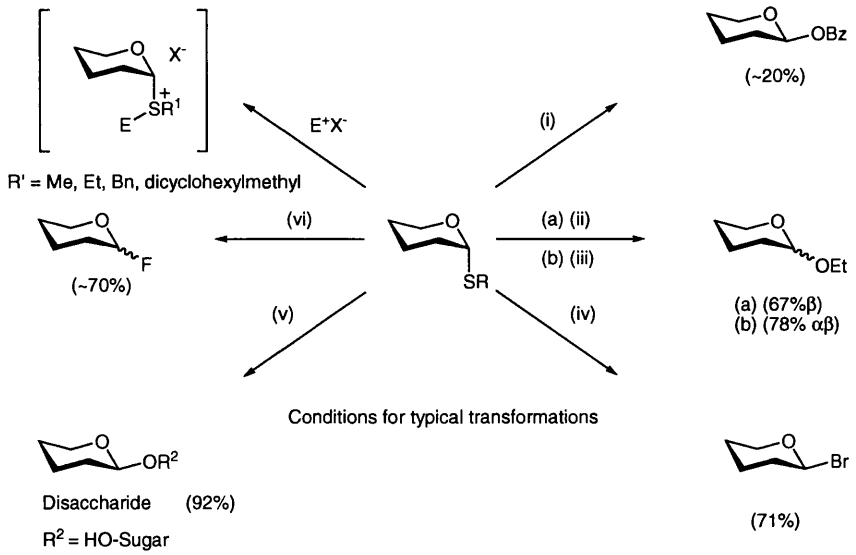
Scheme 51: *Mechanism of thioglycoside synthesis*

Initially thioglycosides were activated using thiophilic metal salts; with mercury (II), lead (II), copper (II) and silver (I) being the most popular.Unfortunately these salts have been shown to be less successful when sugar acceptors are employed in glycosylation strategies. This has necessarily led to the development of a series of non- metallic thiophilic reagents including; NIS/TfOH [165] NIS/TMSOTf,[166]IDCP,[167,168] MeOTf,[1,98,169] and I_2. [170] Glycosylation proceeds in all these cases by attack of an active electrophile (alternatively described as a thiophile) at the sulfur atom forming a sulfonium cation **233**, this labializes the 'thio' moiety turning it into a good leaving group. The lone pair of electrons present upon the glycosides 'ring' oxygen is then involved in the formation of an oxonium ion **234** eliminating the aforementioned leaving group. Subsequent attack of a suitable nucleophilic acceptor results in glycoslation products **235** and **236** (Scheme 52).



Scheme 52: *Electrophilic activation of thioglycosides*

Along with their use in 'direct glycosylations' i.e. in the synthesis of *O*-glycosides, thioglycosides have shown an additional use in the fact that they are readily converted into a range of other glycosyl donors, under a range of mild conditions (Scheme 53). Thioglycosides may also be hydrolyzed catalytically to their corresponding hemiacetal form by the addition of V_2O_5-H_2O_2/NH_4Br.[171]



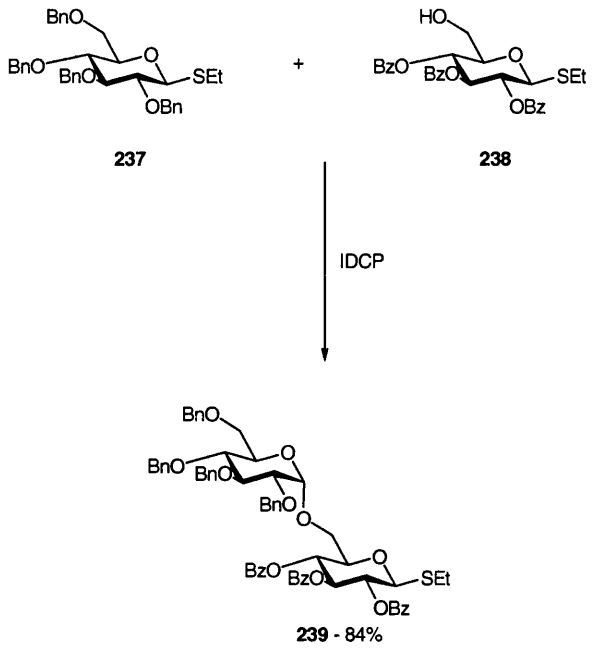
Scheme 53: *Thioglycosides and their reactions*

As previously described, the synthesis and use of thioglycosides has been well documented from the pioneering work of Garregg [158] through to the present day with a publication from Fairbanks and co-workers utilizing 2-*O*-allyl thioglycosides.[172]

2.2 Programmable thioglycosides

One of the most significant uses of thoiglycosides has been in the development of new systems for the development of chemoselectivity in glycosylation reactions. Although originally developed using pentenyl glycosides[76,30,31,173] as donor acceptor combinations, its development towards the use of anomeric thioglycosides has shown enormous potential.

As mentioned earlier chemoselective glycosylations are possible if armed/disarmed glycosides are used where usually the armed glycoside possesses an electron donating C-2 ether functionality capable of activating the glycoside towards behaving as a glycosyl donor whereas the use of an electron withdrawing C-2 ester disarms the glycoside towards glycosyl donor behaviour. Van-Boom and co-workers[174-177] [178] have shown that analogous to the *O*-pentenyl systems thioglycosides may also be activated by the use of C-2 ether protecting groups, whilst a glycoside possessing a C-2 ester protecting group acts to deactivate the glycoside. In their variant the use of glycosyl donor **237**, in the presence of iodonium di-*sym*-collidine perchlorate (IDCP) and disarmed acceptor **238** gave disaccharide **239** in an 84% yield as predominantly the α-anomer (Scheme 54).

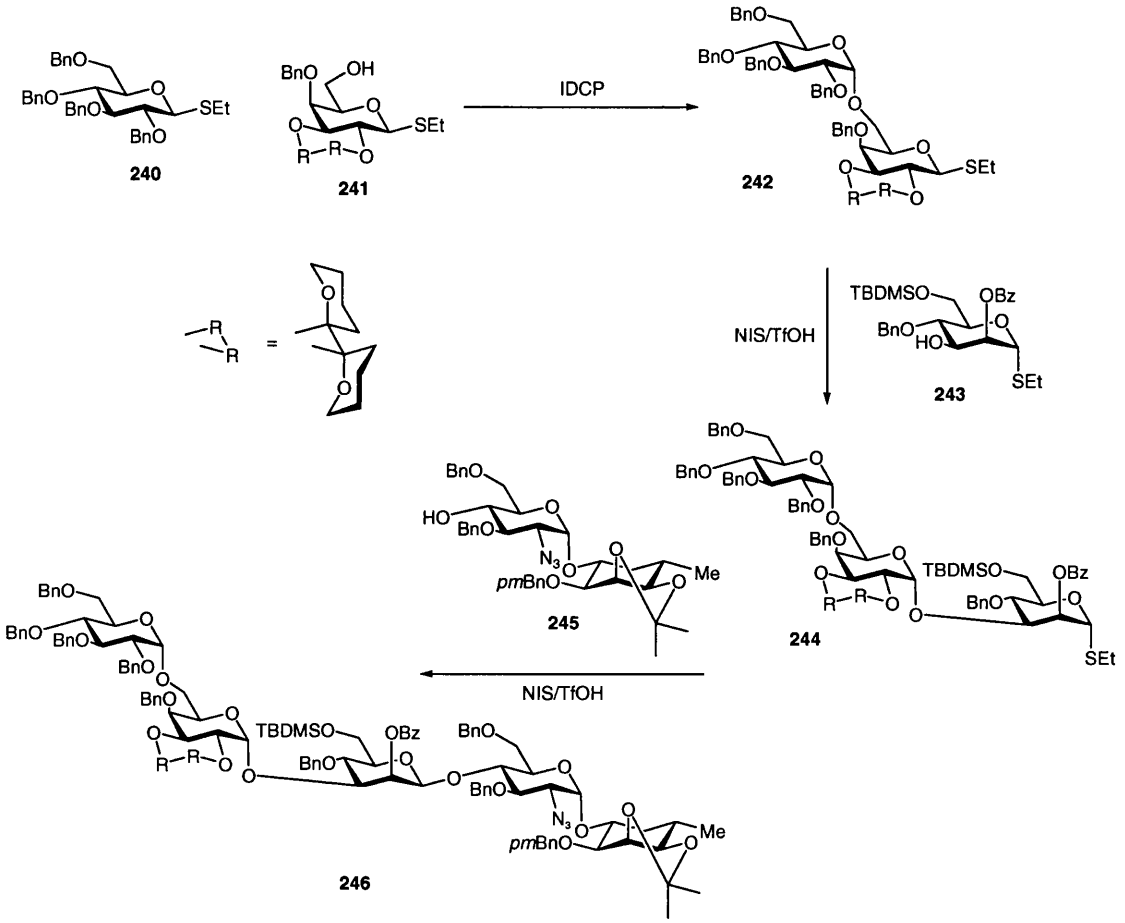


Scheme 54: *Armed disarmed disaccharide synthesis*

It was also discovered that the disaccharide **239** could also be further activated towards glycosylation by use of the more reactive thiophilic activation system NIS/TfOH.

Ley and co-workers have used novel C-2/C-3 dispiroketal protecting group (R-R) to produce a further level of reactivity which has a profound effect on the reactivity of the anomeric centre. It was shown that the use of the dispiroketal **242** produces a glycoside that has reactivity between that of an armed C-2 alkylated thioglycoside and a disarmed C-2 acyl thioglycoside. This varying level of activity was exploited in the synthesis of pentasaccharide **246** which is a protected analogue of a common surface protein of *trypanosome brucei.* Consequently, IDCP mediated chemoselective glycosylation of glycosyl donor **240** with dispiroketal acceptor **241** gave disaccharide **242** in an excellent yield (82% α:β = 5:2). Further activation was achieved by the use of the more powerful thiophilic activator system NIS/TfOH with the torsially deactivated donor **242** and electronically deactivated acceptor **243** giving trisaccharide **244** in a 62% yield as one isomer. The same activation system

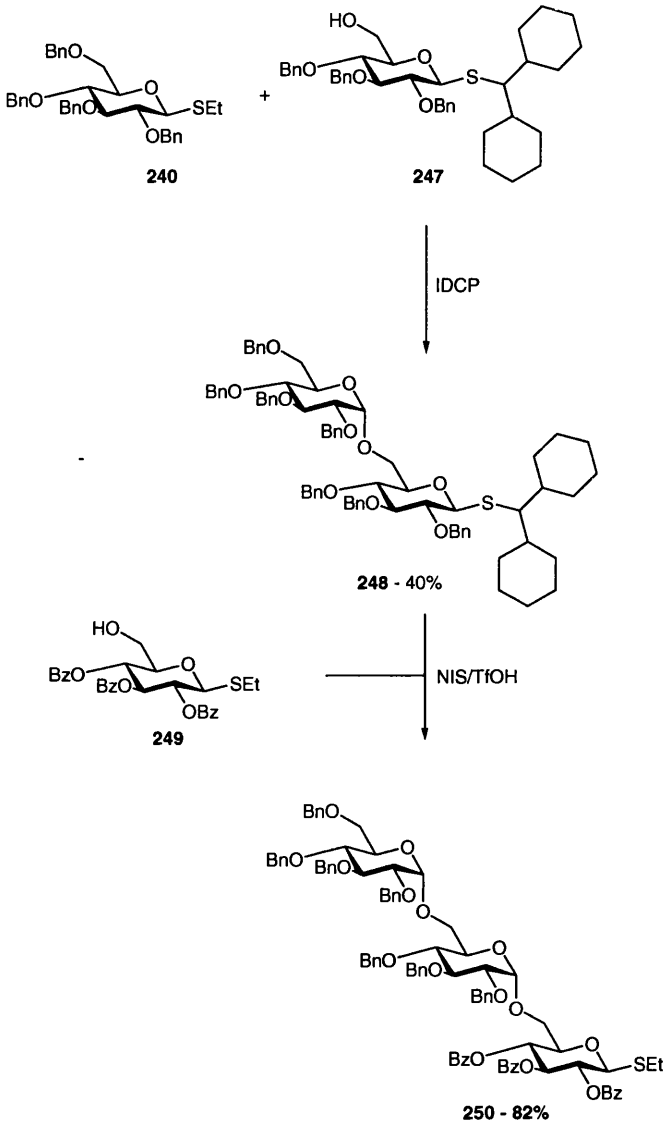
used to generate **244** was employed to couple disaccharide **258** acceptor with trisaccharide donor **244** resulting in the formation of the desired pseudo-pentasaccharide **246**. In this strategy modification of the specific protecting groups allows for chemoselectivity (ether-dispiroketal-ester), but in some circumstances modification of the leaving group itself allows tuning of the anomeric reactivity (Scheme 55).



Scheme 55: *Armed/disarmed dispiroketal glycosides*

This is emplified by the work of Boons and co-workers.[78] It was demonstrated that altering the steric bulk of a glycoside significantly alters the anomeric reactivity of a given glycosyl donor. Hence, IDCP activation of ethyl thioglycoside **240** in the presence of dicyclohexylmethyl thioglycosyl **260** acceptor resulted in the formation of disaccharide **261** in a 79% yield as a single anomer. Further activation of sterically deactivated donor **261** with C-2 benzoylated acceptor **264** in the presence

of the more powerful activator system NIS/TfOH gave trisaccharide **250** in an 82% yield (Scheme 56). No self condensation or polymeric products were identified. These experiments demonstrate clearly the different levels of activation possible with ethyl thioglycosides having a fully armed ether and benzoyl protecting group on C-2.

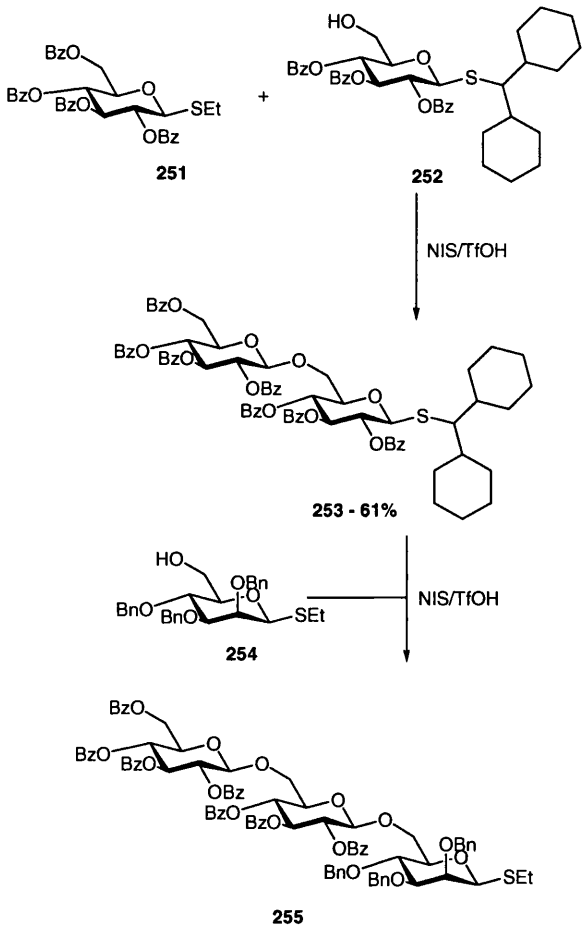


Scheme 56: *Armed/Disarmed trisaccharide synthesis*

This new method provided the methodology for a new series of sterically and electronically modified glycoside building blocks. It intuitively followed that the use of sterically and electronically deactivated glycosyl donor and acceptor **260** and **252** would have a lower reactivity than the sterically and electronically deactivated glycosyl donor **240** and **251** (Scheme 56 and 57). As predicted, coupling of glycosyl

donor **251** with acceptor **252** in the presence of NIS/TfOH gave disaccharide **253** in a 61% yield. Subsequent glycosylation with C-6 mannose based acceptor **254** gave trisaccharide **255** in good yield (Scheme 57). This demonstrated that even this 'doubly' deactivated glycosyl donor is still a suitable glycosyl donor.

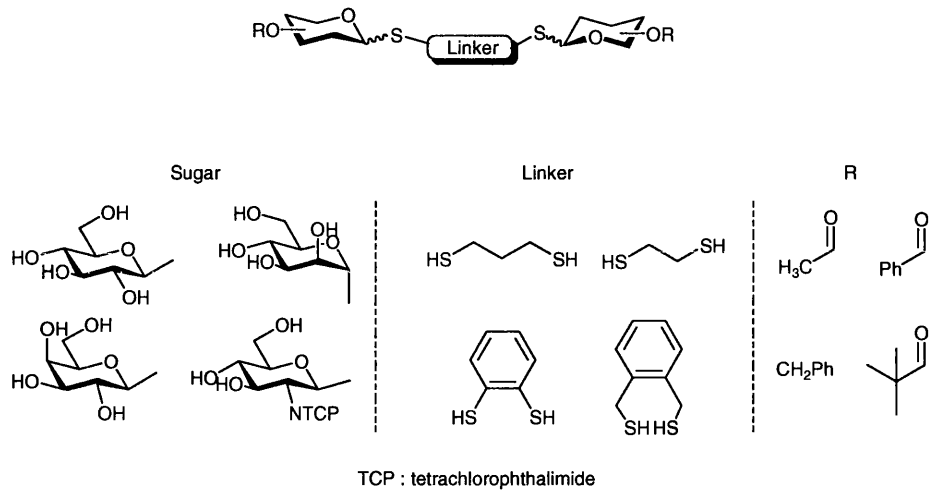
Recently various research groups have been involved researching the effect of altering the leaving group bond on electronic effects and this includes the research depicted in this thesis.



Scheme 57: *Sequential armed/disarmed approach*

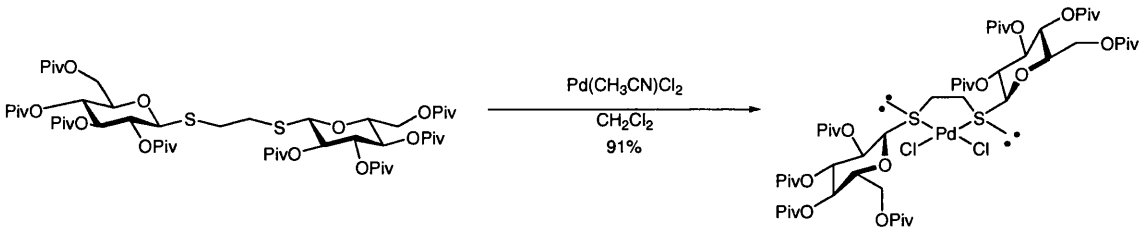
Thioglycosides have also found use in other areas of organic chemistry including their novel use as ligands in asymmetric catalysis. Recently Khair and co-workers have reported the use of *bis*-thioglycosides as ligands in palladium catalysed allylic substitutions.[179] In their strategy Khair and co-workers were interested in three main

areas of ligand design for their *bis*-thioglycosides: the linker, sugar residue and protecting groups thereof were all subject to investigation (Scheme 58).

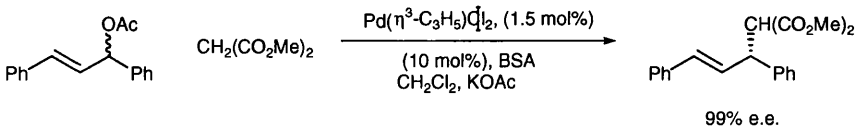


Scheme 58: *Thioglycosides as ligands*

In their report the sugar, linker, and protecting group combination which provided the best yield and enantioselectivity reported was that where glucose was protected with pivolyl groups with an ethane disulfide linker (Scheme 59). This gave the substitution product in 86% and 90% ee in favour of the *S*-enantiomer (Scheme 60) at 0 °C when *bis*-thioglycoside (Scheme 59) was used as a ligand in palladium catalysed allylic substitution.



Scheme 59: *Coordination of thioglycosides*



Scheme 60: *Thioglycosides as ligands for allylic substitutions*

2.3 Novel armed/disarmed glycosylation approaches

The idea of using armed and disarmed glycosyl donors has been heavily described in the literature earlier and has led to rapid development of a number of important oligosaccharides.[180, 181] Although this method offers various levels of activation there is scope to increase the number of levels of activation possible. An approach which could be envisaged to allow further levels of activation would be to use potentially metal binding 'glycosyl ligands' as anomeric activating groups upon glycosyl donors which would allow chemoselective glycosylation due to potentially different binding affinities. A second feature of this strategy would potentially allow the internal delivery of the glycosyl acceptor. As a result of varying the electronic nature of the glycosyl leaving group it may also be possible to increase the number of variable activation levels possible thus creating a reactivity series with a larger number of glycosyl donors with variable activation potentials. (Figure 19).

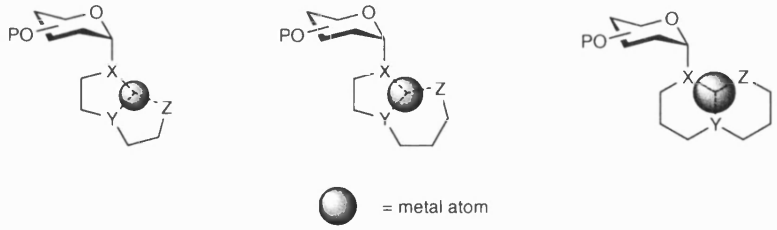
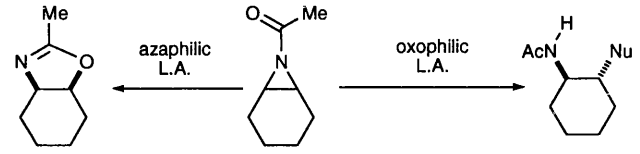


Figure 19: *Coordination approach*

This electronic approach also allows investigations into selective metal binding in a number of different modes. Firstly the use of different heteoatoms gives the potential to allow selective binding by various metal centres. For example, by use of Pearsons hard soft acids and bases theory [182,183] ligands bearing soft sulfur atoms would be expected to be selective towards thiophilic copper ions whilst hard oxygen containing ligands would be expected to prefer oxophilic titanium centres. Also the affinity of a particular ligand with any given metal is perceived to be affected by the

alteration of the metal 'binding pocket' size. This concept has precedence in the work of Lectka [184] who has demonstrated that acylaziridines can be activated towards nucleophilic attack when metals that bind oxygen are used, whereas when metals which bind nitrogen are used then rearrangement is observed (Scheme 61).



Scheme 61: *Coordinating metals*

The idea of utilizing different metals may then in terms of a glycosylation protocol allow for the development of a novel chemoselective glycosylation strategy where selective choice of Lewis acid would allow selective glycosylation to occur. Hypothetically it was also envisaged that a coordination based mechanism may compete with traditional S_N1 and S_N2 based glycosylations. This would then lead to a new breed of glycosyl donors for use in one pot or sequential chemoselective glycosylations. When strategically placed heteroatomic substituents are used as part of the donors this would affect the reaction potential of each donor towards a given Lewis Acid. It was envisaged that glycosylation *via* metal activation of glycosyl donors bearing metal ligands would offer stereocontrol in glycosylation reactions. Also a possibility would be the binding and subsequent intramolecular delivery of the acceptor *via* metal coordination. Thus metals that chelate with differing coordination geometries would allow the direction of acceptor attack to be achieved *via* different trajectories (Figure 20). This type of process for coordination of a glycosyl donor has been described by Koto and co-workers[185] with their use of 2-methoxyethyl glycosides for the *in-situ* generation of anomeric chlorides for subsequent glycosylation by the use of $TiCl_4$.

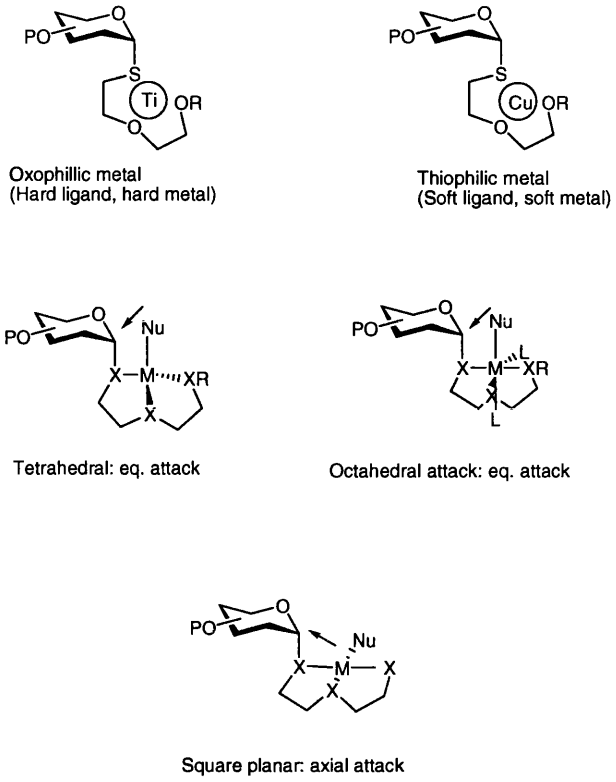


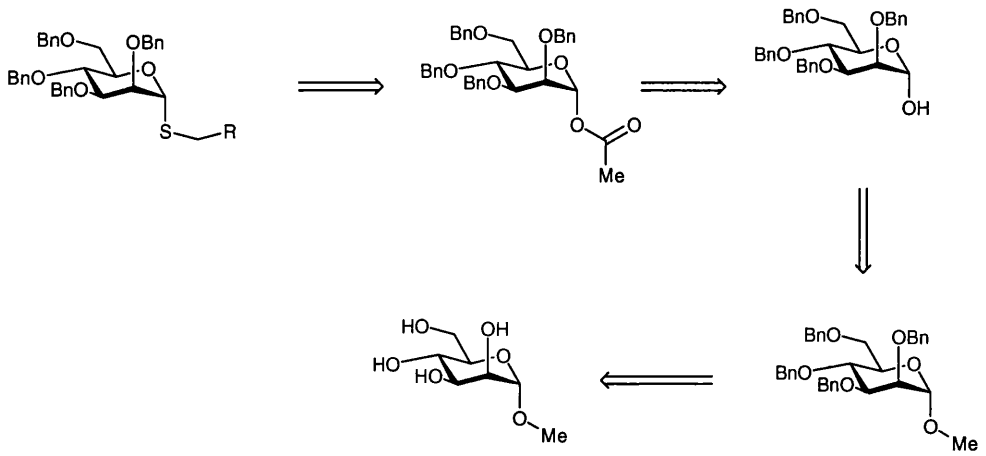
Figure 20: *Metal based 'binding pocket'*

2.4 Synthesis of novel 1-thioglycosides

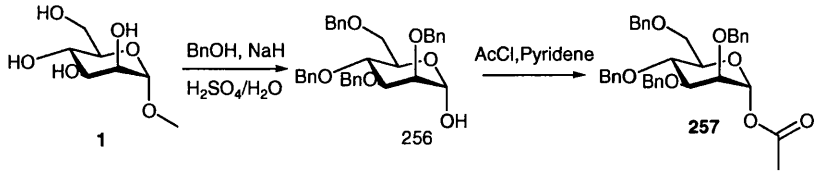
In order to investigate the widest range of factors affecting the glycosylation procedure to be developed it was decided that the best substrates to investigate would be the mannose series due to the relative ease of obtaining the core starting material methyl-α-D-mannopyranoside and the expected high α-selectivity. Chemically this compound would also provide a chance to investigate the glycosylation reaction without steric interference from the presence of either an acyl, benzyl or benzoyl substituent at C-2 due to its axial orientation. It was also decided to initiate this investigation by the production of diheteroatomic thioglycosides where the second heteroatom was either an oxygen, nitrogen or sulfur atom. The use of hetero aromatic substituents would allow for the generation of potentially 5 membered bidentate chelates akin to the chelation pattern described in Figure 20 The easiest route to the generic structure of the target glycosides would then be to employ

aromatic thiols based upon furan, pyridine, and thiophene frameworks. An additional benefit of the mannoside series was that coordination to the metal centre *via* the two heteroatoms would potentially deliver the acceptor via the β-face of the glycosyl donor. The axially positioned C-2 protected substituent prevents interference from any protecting group, which is a feature not applicable to equatorially positioned substituents as in, for example, glucose type glycosides.

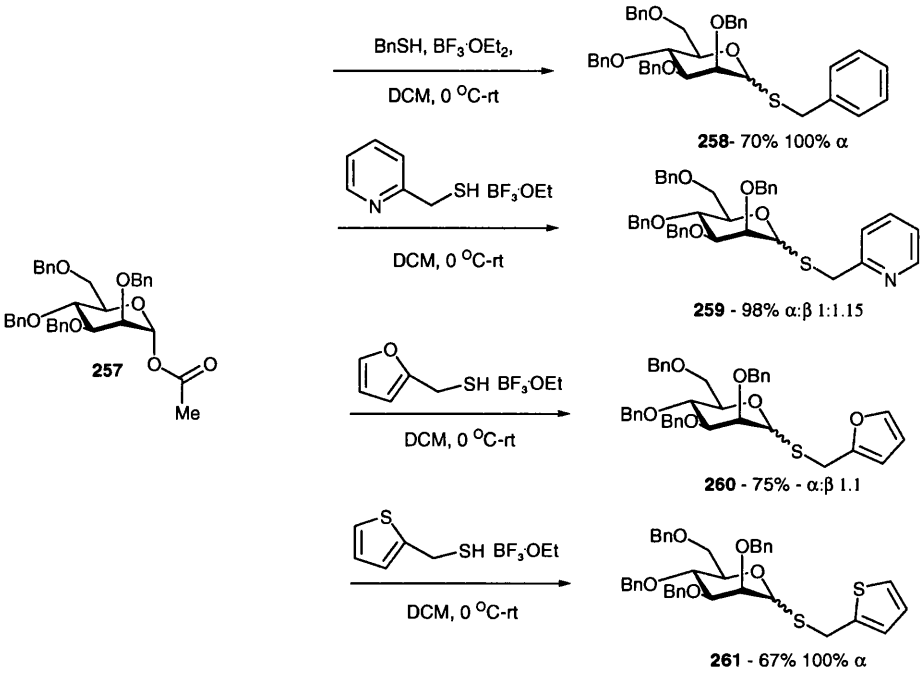
The synthetic route to these compounds is shown in the retrosynthetic analysis depicted in Scheme 62. This would entail the use of benzyl protecting groups to generate armed glycosides in a four step procedure starting from the core material methyl-α-D-mannopyranoside. Thus it was envisaged that benzyl protection of **1** followed by acidic hydrolysis of the methoxy acetal would generate the tetrabenzylated pyranose. Subsequent acetylation of this would provide the suitably labile glycosyl donor (Scheme 63) which, when reacted with the appropriate thiols, would result in the formation of thioglycosides **258-261** under Lewis acidic conditions (Scheme 64). The production of the benzyl thioglycosides **258** as a useful armed glycosyl donor would for our purposes act as a control compound to allow comparisons to be made with potentially chelating glycosides.



Scheme 62: *Retrosynthetic analysis for thioglycoside synthesis*



Scheme 63: *Formation of 1-O-acetyl mannoside 257*



Scheme 64: *Novel thioglycoside synthesis*

The preliminary benzylation step was performed initially using the procedure by Koto and co-workers[186] whereby benzyl chloride was first added to **1** and to this was subsequently added sodium hydride. This resulted in a 85% yield of the tetra-*O*-benzylated mannopyranoside following column chromatography. ^{1}H-NMR analysis identified the benzylated material showing distinctive signals for the methoxy protons (3H singlet at 3.2 ppm), a 20H multiplet between 7.1 and 7.5 ppm and the expected α-anomeric signal (1H doublet at 5.1 ppm). Further confirmation by HRMS analysis gave the molecular ion at 572.3013 Da ($M+NH_4$). Due to the high reaction temperatures and amounts of benzyl chloride used this method was replaced with the universally used conditions which employ the use of five equivalents of benzyl bromide with sodium hydride as the base and DMF as the reaction solvent [187]

the reaction was carried out at room temperature. Yields and reaction times were comparable to the initial methodology.

Acid hydrolysis of the tetrabenzylated methoxymannoside was performed by the addition of 3M sulfuric acid in acetic acid at 80 °C which gave **256** in a 85% yield after 30 minutes, again ^{1}H-NMR analysis indicated the production of **256** by the disappearance of the methoxy signal at 3.2 ppm and shift in anomeric signal to a higher field value of 5.22 ppm. HRMS identified the molecular ion 558.2850 Da ($M+NH_4$), and the free alcohol functionality was confirmed by IR analysis, with a characteristic broad signal appearing at 3413cm^{-1}.

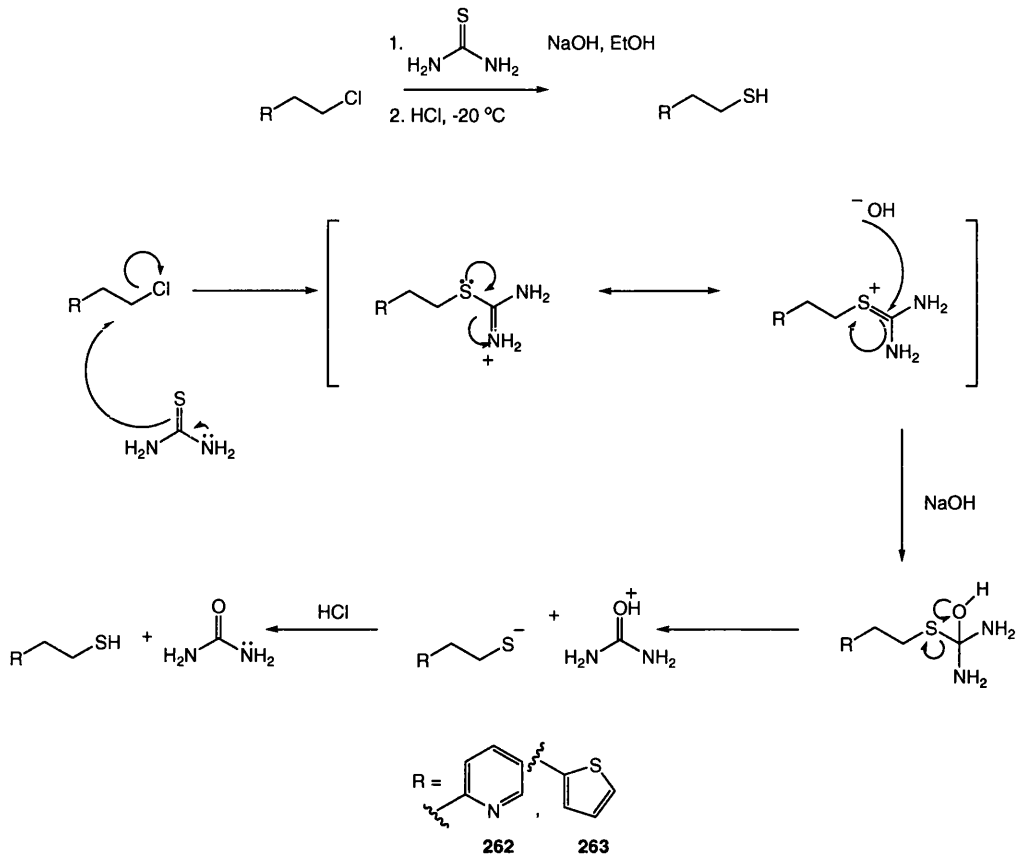
Acetylation of the hemiacetal functionality was readily accomplished with acetyl chloride in DCM solution using pyridine as base. The reaction was typically complete in 90 minutes and subsequent purification by flash chromatography yielded the acetylated mannopryanoside **257** in 82%. Identification of the product was confirmed by the presence of the acetyl methyl 3H singlet at 2 ppm and a 1H doublet indicating the α-anomer at 6.2 ppm in the proton NMR. The molecular ion of 600.2961 Da ($M+NH_4$) was observed by HRMS. The disappearance of the alcoholic function in the IR spectrum and appearance of a strong intensity carbonyl band at 1750 cm^{-1} also confirmed the identity of the acetylated product. All the above reactions were successfully carried out on a multi gram scale, starting with up to 12 g of the initial starting material **1**.

With glycosyl donor **257** readily at hand glycosylations with the commercially available benzyl and furfuryl mercaptans were first attempted. Following the basic methodology by Boons and co-workers[164] this involved the use of TMSOTf as the Lewis acid. Using acetate **257** and 1.5 equivalents of thiol and 1.1 equivalents of the TMSOTf at 0 °C, reactions were typically complete in 3 hours. This methodology

produced the benzyl and furfuryl thioglycosides in 70% and 49% yield respectively. Both compounds were identified by their ^{1}H-NMR spectra comparing the shift upfield resulting from the change in anomeric signal from 6.2 for the acetate to 5.21 ppm for the benzyl thioether **258** and 5.31 ppm for the furfuryl thioether **260**. Furthermore the increase in benzyl protons shown for the benzyl mercaptan by the integrals shown and the presence of 1H proton signals of the furan ring at 6.2 and 6.3 ppm were characteristic HRMS also indicated the presence of molecular ion, for thioglycoside **258** giving 646.2716 Da ($M+NH_4$) and for thioglycoside **260** 664.3099 Da ($M+NH_4$) were observed. However this method resulted in a reaction mixture which was difficult to purify by flash chromatography with a series of successive purification steps generally required in order to produce acceptable material for further use. As a result we switched to the use of the alternative Lewis acid boron trifluoride diethyl etherate $BF_3{\cdot}OEt_2$. Typically we used equivalent conditions to that used for the TMSOTf methodology with the only variations being the Lewis acid and quenching technique. This method resulted in a general increase in the yield of the reaction with an 81% in the case of the benzyl thioglycoside and between 55-75% for that of the furfuryl variant.

With the successful preparation of the two initial test thioglycosides, our efforts then turned towards the production of the pyridyl and thiophenyl versions. Unfortunately at this time neither was commercially available so routes for their syntheses were necessary. Initially, searches revealed several literature precedents.[188,189] In both cases preparation of the corresponding thiols was difficult and in the case of the mercaptomethyl thiophene compound **263** yields were low, generally between 15 and 20 %. In the case of the mercaptomethyl pyridine variant **262** a 68% yield was the best achieved but reproducibility was problematic. The thiol was identified by a

characteristic medium intensity S-H stretch at 2530.8 cm^{-1} and NMR data which matched that observed in the literature. [189] For the case of the thiophene based mercaptan unidentified polymerization products arose frequently, resulting in an attempted modification of the procedure by converting the thiophene methanol starting material into the corresponding chloride and triflates. Treatment of 2-thiophenemethanol with 1.1 equivalents of thionyl chloride in DCM at 0 °C gave the intermediate chloride identified by IR spectroscopy from the characteristic C-Cl bend at 1255.2 cm^{-1}. Subsequent addition of thiourea in ethanol to either of the chlorides (Scheme 65) resulted in the formation of the thioether intermediate *via* nucleophilic substitution of the halide. Hydrolysis of this was achieved by the addition of sodium hydroxide. This gave the mercaptan in a 15% crude yield. However significant amounts of an unidentified black tar like substance suspected to be polymerization/oligomerisation material also resulted, with the thiophene thioglycoside **261**. Subsequent attempts to purify either by flash chromatography or by vacuum distillation resulted in degradation of the product or polymerization to a black tar like substance. Several attempts were made to modify this procedure including performing the reaction at high dilution in order to attempt to minimize the suspected polymerization problem but this proved to be unsuccessful. Direct nucleophilic substitution of the chloride and methoxy thiophene compounds by the addition of sodium sulphide in ethanol was also attempted, however no reaction took place.



Scheme 65: *Mechanism for thiol synthesis*

Although much of the work on production of the two required thiols proved unsuccessful, sufficient crude product was generated in order to attempt glycosylation with anomeric acetate **257**. As a result the addition of 1.5 equivalents of crude thiols to the acetate in DCM at 0 °C in the presence of 1.1 equivalents of $BF_3{\cdot}OEt_2$ resulted in the production of both the 1-thiophenyl **261** and 1-pyridyl thioglycosides **259** in 46 and 65% yields respectively. In the case of the latter this was the first significant case for production of both α and β-anomers as evidenced by TLC analysis, in these types of glycosylations. Initially separation of the two anomers of **259** proved unsuccessful so initial glycosylation trials were carried out upon this mixture which comprised of a 1:1.15 (α:β) mixture of anomers as identified by ^{1}H-NMR spectroscopy the spectrum displayed characteristic doublets at 5.35 ppm for the α-anomer and 4.60 ppm for the β-anomer with coupling constants of 2 and 1

Hz respectively. Also indicating the presence of the desired product was the identification of the molecular ion from the HRMS of 648.2782 Da (M+H) for the α-anomer and 648.2788 Da (M+H) for the β-anomer. The thiophene thioglycoside produced was predominantly the α-anomer with thiophene signals present between 6.88 and 6.97 ppm as a 3H m and the α-anomeric signal present at 4.91 ppm as a doublet with a coupling constant of 2 Hz.

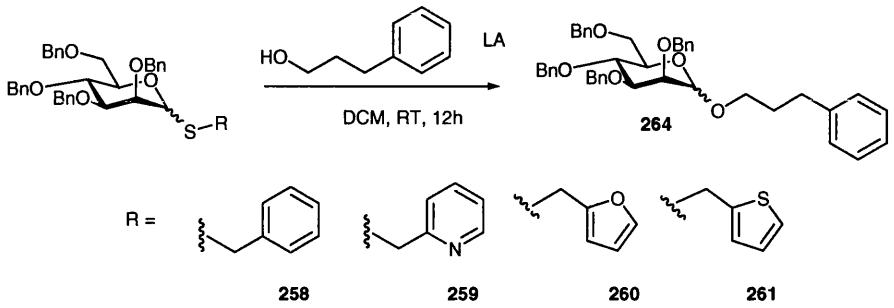
At a later date both the pyridyl and thiophene mercaptans became commercially available. Subsequent use of these sources of the mercaptans allowed for increased yields of each thioglycoside to 67% and 95% for the thiophene and pyridyl systems respectively. In the case of the pyridyl glycoside an anomeric ratio of 1:1.15 (α:β) was observed. The anomers of the pyridyl thioglycoside **259** later became separable by flash chromatography but with the use of 'oversized' flash chromatography.

2.5 Lewis acid mediated glycosylation study

With the initial glycosides in-hand it was decided to concentrate on studying the reaction of each of the thioglycosides with a variety of different Lewis acids. It was decided that the initial glycosylation studies would concentrate on the use of 3-phenylpropanol as the glycosyl acceptor for several reasons. Firstly the use of an unhindered primary alcohol should allow for favourable formation of 2, 3, 4, 6-tetra-*O*-benzyl-α/β-D-1-*O*-propylphenylmannopyranoside **264**. Secondly the choice of acceptor would allow facile product identification due to peaks for the of alkyl residues being present away from both the aromatic and pyranosyl ring regions of the ^{1}H-NMR spectrum that would be produced.

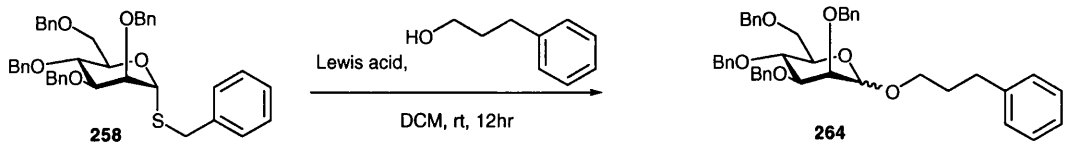
Initially it was decided to concentrate upon glycosylations at an ambient temperature and to use a non participating reaction solvent, (dichloromethane was the preferred

choice). The standard conditions were the addition of 1.1 equivalents of Lewis acid and the use of 2.2 equivalents of 3-phenyl propanol as the glycosyl acceptor. For the benefit of rate comparisons a standard 12 hour reaction time was adopted in initial trials (Scheme 66).



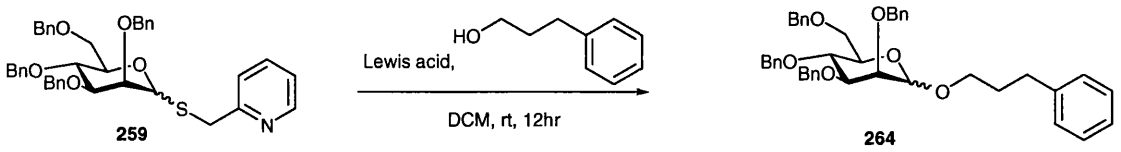
Scheme 66: *Lewis acid glycosylation study*

The initial selection of Lewis acids covered a range of elements considered to posses various degrees of 'Hardness' and 'Softness' according to Pearson's hard and soft rule for acids and bases (HSAB theory). Typical hard Lewis acids used were the series based upon titanium tetraisopropoxide and titanium tetrachloride, including the monochloride triisopropoxide, dichloride diisopropoxide and the trichloride monoisopropoxide all prepared *via* a disproportionation reaction between the parent titanium tetraisopropoxide and titanium tetrachloride in the appropriate ratios. With the exception of the titanium isopropoxide it was found that these Lewis acids were too reactive for the glycosyl donors used in this study and an unidentifiable black material resulted in each case. When titanium tetraisopropoxide was used column chromatography allowed for the recovery of the initial starting materials for each thioglycoside investigated but no product could be detected. Examples of soft Lewis acids used were the lanthanide triflates of ytterbium and neodymium. Unfortunately in these cases neither Lewis acid produced glycosylated product for any of the four thioglycosides investigated. Tables 5 to 8 display results generated for each thioglycoside investigated.



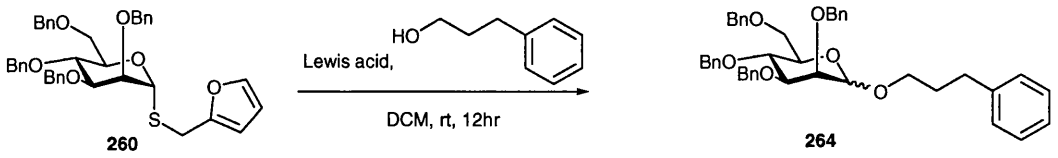
Glycoside	Lewis Acid	Yield
258	$Ti(O^iPr)_4$	No reaction
258	$Ti(O^iPr)_2Cl_2$	BSM
258	$Ti(O^iPr)Cl_3$	BSM
258	$Ti(O^iPr)_3Cl$	BSM
258	$Ni(ClO_4)_2 \cdot 6H_2O$	No reaction
258	$Cu(OTf)_2$	No reaction
258	$Zn(OTf)_2$	No reaction
258	$Yb(OTf)_3$	No reaction
258	$Nd(OTf)_3$	No reaction
258	ZnI_2	No reaction
258	$HgCl_2$	No reaction

Table 5: *Room temperature Lewis acid study for* ***258***



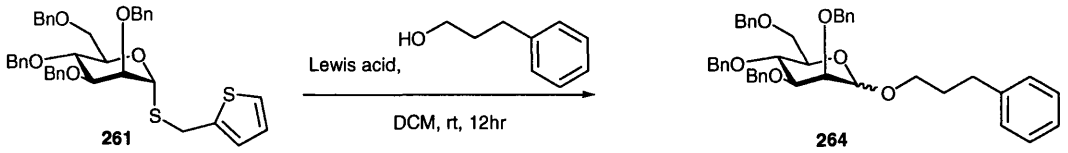
Glycoside	Lewis Acid	Yield
259	$Ti(O^iPr)_4$	No reaction
259	$Ti(O^iPr)_2Cl_2$	BSM
259	$Ti(O^iPr)Cl_3$	BSM
259	$Ti(O^iPr)_3Cl$	BSM
259	$Ni(ClO_4)_2 \cdot 6H_2O$	No reaction
259	$Cu(OTf)_2$	26% 100%α
259	$Zn(OTf)_2$	No reaction
259	$Yb(OTf)_3$	No reaction
259	$Nd(OTf)_3$	No reaction
259	ZnI_2	No reaction
259	$HgCl_2$	No reaction

Table 6: *Room temperature Lewis acid study for* ***259***



Glycoside	Lewis Acid	Yield
260	$Ti(O^iPr)_4$	No reaction
260	$Ti(O^iPr)_2Cl_2$	BSM
260	$Ti(O^iPr)Cl_3$	BSM
260	$Ti(O^iPr)_3Cl$	BSM
260	$Ni(ClO_4)_2 \cdot 6H_2O$	No reaction
260	$Cu(OTf)_2$	No reaction
260	$Zn(OTf)_2$	No reaction
260	$Yb(OTf)_3$	No reaction
260	$Nd(OTf)_3$	No reaction
260	ZnI_2	No reaction
260	$HgCl_2$	No reaction

Table 7: *Room temperature Lewis acid study for* ***260***



Glycoside	Lewis Acid	Yield
261	$Ti(O^iPr)_4$	No reaction
261	$Ti(O^iPr)_2Cl_2$	BSM
261	$Ti(O^iPr)Cl_3$	BSM
261	$Ti(O^iPr)_3Cl$	BSM
261	$Ni(ClO_4)_2 \cdot 6H_2O$	No reaction
261	$Cu(OTf)_2$	No reaction
261	$Zn(OTf)_2$	No reaction
261	$Yb(OTf)_3$	No reaction
261	$Nd(OTf)_3$	No reaction
261	ZnI_2	No reaction
261	$HgCl_2$	No reaction

Table 8: *Room temperature Lewis acid study for* ***261***

Following this initial study it was discovered that at room temperature copper (II) triflate mediated the reaction with 1-pyridylthioglycoside (**259**) to give the corresponding α 1-*O*-glycoside **264** in 26% yield. This derivative was identified by ^{1}H-NMR spectroscopy, the presence of propyl 2H multiplets between 1.7 and 1.8 ppm, 2.5 and 2.6 ppm and alpha anomeric H^1 doublet at 4.77 ppm with a coupling constant of 3 Hz. An interesting feature of this type of ^{1}H-NMR spectrum is the loss of symmetry and hence equivalence resulting from the coupling of even simple alcohols with any given glycosyl donor. This is evident here by the splitting of the two proton signals present on the alkoxy carbon of 3-phenyl propanol due to the proximity of proton H(37) (Figure 21) to not only the anomeric oxygen but also the pyranosyl ring oxygen. These protons are described as diastereotopic. This results

in the H(37) ^{1}H signal being located further downfield with respect to that of H(38) which is seen as part of a complex multiplet with H(42) and H(43) i.e. H2 and H3 under normal notation of monosaccharides.

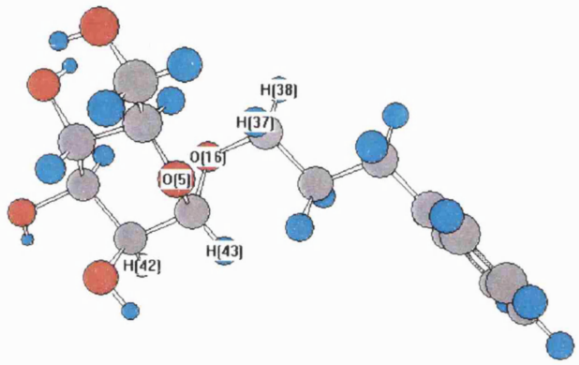
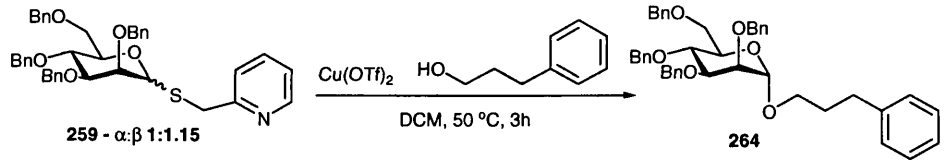


Figure 21: *3D model of* ***264***

From the glycosylation experiments mediated by copper (II) triflate interesting empirical observations could be made. Dramatic colour changes were observed, for example when 1-*S*-pyridyl thioglycoside was used as the donor. Upon addition of copper(II) triflate a distinct emerald green colour was immediately observed. This suggested that there may be coordination taking place either at the sulfur or *via* the desired 5-membered chelate discussed previously. One of the main properties of thioglycosides is that they react readily with electrophilic species in order to produce sulfonium ions as intermediates. These stable intermediates are known to react readily with a wide range of nucleophilic reagents. The other mechanistic alternative open to us at this time was the desired 5-membered chelate suggested in the original project proposal which incorporates the idea that the pyridyl functionality may be involved in a chelation *via* the sulfur and pyridine nitrogen. The acceptor then attacks

either directly at the anomeric carbon in a S_N1 or S_N2 fashion or the alcohol itself binds to the Lewis Acid and is delivered internally from the metal centre of the Lewis acid. If either of these situations were responsible for the colouration observed then the low yield would then suggest that the barrier for the reaction is not activation of the thioglycoside but the addition of the acceptor itself. As a result of this, it was decided optimise the system based upon copper (II) triflate with the 1-pyridylthio mannoside as the donor at higher temperatures, thus, it was decided to increase the temperature to 50 °C. Upon doing so the yield of the reaction was increased initially to 65%. Other acceptors were also investigated at this point, initially cyclohexanol, 2-propanol and 4-penten-1-ol using the 1:1.15 mixture of pyridyl thioglycoside **259.** The results of which are summarized in Table 9.



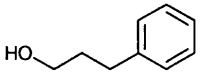
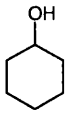
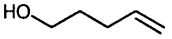
Glycoside	Acceptor	Yield
259		65 (100% α)
259		52 (100% α)
259		63 (100% α)
259		61 (100% α)

Table 9: *Glycosyl acceptor trial for 259*

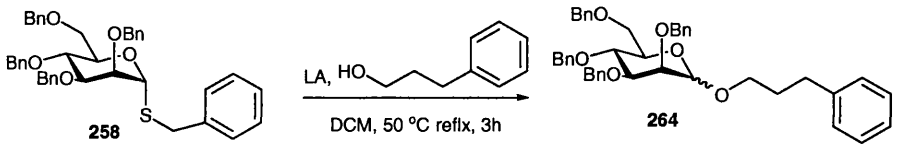
Following the encouraging results displayed in Table 9, efforts were focused towards the use of promoter systems which would show selectivity towards the other thioglycoside donor systems including the control glycoside system, benzyl thioglycoside **258**. This work was aided considerably by the ability to use High

Performance Liquid Chromatography with Mass Spectroscopy capabilities (LC-MS) which allows better control over identifying our initial product **264** rather than Thin Layer Chromatography (TLC). For reactions involving donors **258**, **260** and **261** TLC is often inconclusive due to very little difference in R_f values between the thioglycoside starting materials, the *O*-glycoside product and the evolved thiol although differences in colour are observed when vanillin is used as a staining agent showing a deep green colour for the thiol and brown colour for the *O*-glycoside.

The use of LC-MS as an analytical tool was valuable for the generation of a large number of results in a short period. The reaction conditions employed were those used for the increased temperature trials used on glycosyl donor **259**. Thus 0.009 mmol of thioglycoside, 0.01 mmol of acceptor and 0.01 mmol of Lewis acid were reacted in dichloromethane solution at 50 °C reflux. The reactions were carried out under a nitrogen atmosphere and dry solvents were used throughout. The results are shown per thioglycoside in Tables 10-14. In total twenty one Lewis acid combinations were carried out on each of the thioglycosides **259** and **261** whilst eighteen Lewis acids were used with thioglycosides **258** and **260**.

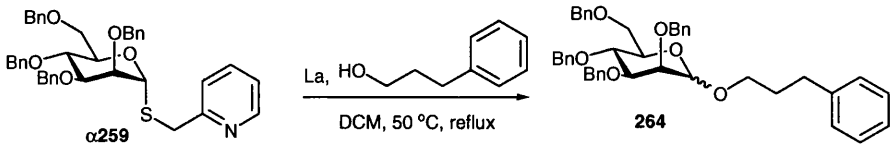
The results displayed in the tables below are encouraging. For example the increase in yield observed for the glycosylation with copper (II) triflate was pleasing. With the pyridyl thioglycoside donor **260** an 85% yield for the α-pyridyl thioglycoside anomer and a 93% yield for the β-pyridyl thioglycoside was obtained. The corresponding glycosylation trial for the benzyl analogue demonstrated that this donor displays no reactivity towards this system. Importantly therefore, this represents the basis for a selective glycosylation system. Also intriguing was the result where the furfuryl based thioglycoside gave a 76 % yield when erbium (III) triflate was the Lewis acid of choice which was also unreactive towards the benzyl

control. In comparison thioglycoside **259** displayed no reaction towards this Lewis acid system. The reactivity of the furfuryl thioglycoside towards $Cu(OTf)_2$ is unfortunate but it is still encouraging in terms of our aims to develop a chemoselective glycosylation strategy i.e. addition of each donor at specific times in order to eliminate competing reactions between both donors and acceptors which react under identical conditions.



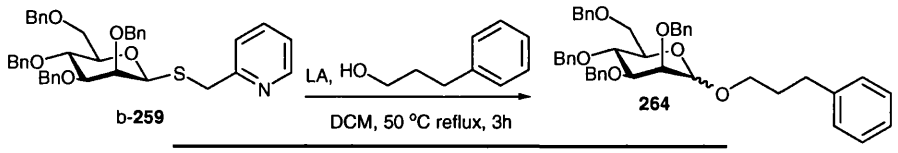
Glycoside	Lewis Acid	Yield
258	$Ti(O^iPr)_4$	No reaction
258	HgI_2	No reaction
258	$Hg(OAc)_2$	No reaction
258	NiI_2	No reaction
258	$Ni(ClO_4)_2$	No reaction
258	AgOTf	48 (100%α)
258	ZnI_2	No reaction
258	$Pr(OTf)_3$	No reaction
258	$Nd(OTf)_3$	No reaction
258	RbI_3	No reaction
258	AuI	47 (100% α)
258	AuI_3	No reaction
258	CoI_2	No reaction
258	$Cu(OTf)_2$	No reaction
258	$Hf(OTf)_4$	No reaction
258	$La(OTf)_3$	No reaction
258	$In(OTf)_3$	No reaction
258	$Er(OTf)_3$	No reaction

Table 10: *50 °C Lewis acid study for 258*



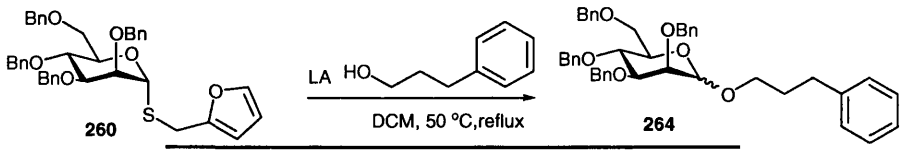
Glycoside	Lewis Acid	Yield
α-259	$Hf(OTf)_4$	No reaction
α-259	AgOTf	No reaction
α-259	$Yt(OTf)_2$	No reaction
α-259	$Er(OTf)_3$	No reaction
α-259	$Ho(OTf)_3$	No reaction
α-259	$Eu(OTf)_3$	No reaction
α-259	$Tm(OTf)_3$	No reaction
α-259	$Cu(OTf)_2$	85 (100% α)
α-259	$Sc(OTf)_3$	No reaction
α-259	ZnI_2	No reaction
α-259	$La(OTf)_3$	No reaction
α-259	$In(OTf)_3$	No reaction
α-259	$Zr(Cp)_2Cl_2$	No reaction
α-259	$Ni(Cp)_2$	No reaction
α-259	$Nd(OTf)_3$	No reaction
α-259	AuI_3	33 (100% α)
α-259	AuI	35 (100% α)
α-259	$Mg(OTf)_2$	No reaction
α-259	$Sn(OTf)_2$	No reaction
α-259	$V(acac)_2$	No reaction
α-259	$AlCl_3$	No reaction

Table 11: *50 °C Lewis acid study for α-259*



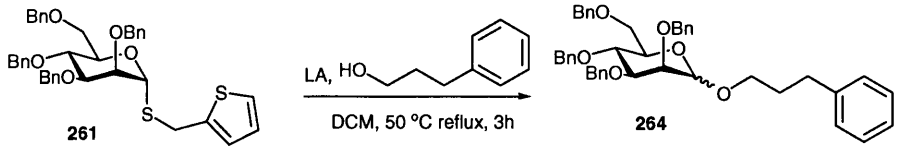
Glycoside	Lewis Acid	Yield
β-259	$Hf(OTf)_4$	No reaction
β-259	AgOTf	No reaction
β-259	$Yt(OTf)_2$	No reaction
β-259	$Er(OTf)_3$	No reaction
β-259	$Ho(OTf)_3$	No reaction
β-259	$Eu(OTf)_3$	No reaction
β-259	$Tm(OTf)_3$	No reaction
β-259	$Cu(OTf)_2$	93 (100% α)
β-259	$Sc(OTf)_3$	No reaction
β-259	ZnI_2	No reaction
β-259	$La(OTf)_3$	No reaction
β-259	$In(OTf)_3$	No reaction
β-259	$Zr(Cp)_2Cl_2$	No reaction
β-259	$Ni(Cp)_2$	No reaction
β-259	$Nd(OTf)_3$	No reaction
β-259	AuI_3	31 (100% α)
β-259	AuI	38 (100% α)
β-259	$Mg(OTf)_2$	No reaction
β-259	$Sn(OTf)_2$	No reaction
β-259	$Vo(acac)_2$	No reaction
β-259	$AlCl_3$	No reaction

Table 12: *50 °C Lewis acid study for β-259*



Glycoside	Lewis Acid	Yield
260	$Ti(O^iPr)_4$	No reaction
260	HgI_2	No reaction
260	$Hg(OAc)_2$	No reaction
260	NiI_2	No reaction
260	$Ni(ClO_4)_2$	No reaction
260	AgOTf	No reaction
260	ZnI_2	No reaction
260	$Pr(OTf)_3$	No reaction
260	$Nd(OTf)_3$	No reaction
260	RbI_3	No reaction
260	AuI	No reaction
260	AuI_3	No reaction
260	CoI_2	No reaction
260	$Cu(OTf)_2$	96 (100% α)
260	$Hf(OTf)_4$	22 (100% α)
260	$La(OTf)_3$	No reaction
260	$In(OTf)_3$	29 (100% α)
260	$Er(OTf)_3$	76 (100% α)

Table 13: *50 °C Lewis acid study for **260***



Glycoside	Lewis Acid	Yield
261	$Hf(OTf)_4$	48 (100% α)
261	AgOTf	37 (100% α)
261	$Yt(OTf)_2$	No reaction
261	$Er(OTf)_3$	No reaction
261	$Ho(OTf)_3$	No reaction
261	$Eu(OTf)_3$	No reaction
261	$Tm(OTf)_3$	No reaction
261	$Cu(OTf)_2$	20 (100% α)
261	$Sc(OTf)_3$	45 (100% α)
261	ZnI_2	No reaction
261	$La(OTf)_3$	No reaction
261	$In(OTf)_3$	No reaction
261	$Zr(CP)_2Cl_2$	No reaction
261	$Ni(CP)_2$	No reaction
261	$Nd(OTf)_3$	No reaction
261	AuI_3	No reaction
261	AuI	No reaction
261	Mg(OTf)	No reaction
261	$Sn(OTf)_2$	No reaction
261	$Vo(acac)_2$	No reaction
261	$AlCl_3$	No reaction

Table 14: *50 °C Lewis acid study for* ***261***

Separation of the product anomers for the pyridyl thioglycoside **259** was to prove difficult. Separation was eventually possible by using very large ratios of silica to crude product in flash chromatography. Typically ratios of 150:1 (mass of silica: mass of product mixture) or greater were necessary to achieve separation, in contrast to the 20:1 to 100:1 ratios normally recommended for column chromatography.[190,191] The two anomers of glycosyl donor **259** could be identified by TLC analysis and had R_f values of 0.37 and 0.32 when an eluent composition of 7:3 petrol: ethyl acetate was used for the pyridyl thioglycoside and the ^1H signal for the α-anomer at 5.35 ppm and a $J^{1,2}$ coupling constant of 2 Hz and the β-anomer at 4.60 ppm with a $J^{1,2}$ coupling constant 1Hz in the ^1H-NMR spectrum. Both anomers of donor **259** also gave the corresponding molecular ion when subjected to electron ionization high resolution mass spectroscopy with the α anomer giving a molecular ion of $(M+H)^+$ 648.2788 and the β anomer giving a value of $(M+H)^+$ 648.2782. The separation of the two anomers of **259** allowed comparisons to be made as to the reactivity similarities and differences between the two pyridyl thioglycoside anomers as was described earlier for the bromo glycosides where pre equilibrium was set up between the two corresponding anomeric bromides but glycosylation proceeds faster with the β-bromide. It was also important to attempt to ascertain the reaction mechanism by which this glycosylation was proceeding. This could proceed *via* our proposed coordination type mechanism, the traditional S_N1 type mechanism *via* oxonium ion formation or *via* the corresponding S_N2 type displacement of the pyridyl thiol moiety resulting in the formation of the corresponding β-mannoside. In order to give more information an NMR scale experiment was conducted where a 1:1 mixture of pyridyl thioglycoside was used in CD_2Cl_2. The change in resonance observed for the five protons of the pyridine ring which is clearly identified as a triplet of doublets at 7.47

and a doublet of 8.47 at ppm was monitored. However, this attempt identify the presence of a coordinated intermediate resulted in substantial signal broadening in the ^{1}H-NMR spectrum as a result of the paramagnetism arising from the d^9 electronic configuration of copper(II) complexes. Several re-crystallisation techniques were also attempted in order to crystallise a coordinated intermediate but these proved unsuccessful. The anomeric composition of the pyridyl thioglycoside **259** was also ascertained by the use of C-H coupling constants. As a general rule there is approximately a 10-15 Hz difference in C-H coupling constant for C-1 – H-1 of α and β anomers, with the α anomer showing a higher coupling constant. In the case of the α-pyridyl thioglycoside **259** a coupling constant of 191 Hz was observed whilst for the case of the β-anomer the value was 176 Hz. [192]

At this point it seemed prudent to extend our knowledge of the reactivity of the pyridyl thioglycoside incorporate a wider range of acceptors including those based on sugar donors. Thus, the use of various suitable acceptors displaying a wide range of structural features was attempted; the results of which are displayed in Table 12. For the simple alcohols the yields are very encouraging, but for each case with the exception of the use of methanol the anomeric outcome was estimated by ^{1}H-NMR experiments to be greater than 20:1 in favour of the α-anomer. In the case of methanol the yield was 96%. Confirmation of the anomeric configuration was achieved by a combination of ^{1}H NMR and ^{1}H-^{1}H COSY spectroscopy which showed the α proton signal at 5.12 ppm with a coupling constant of 2 Hz which is comparable to that observed in the literature for the 1-*O*-methoxymannoside.[193]

As described in Table 12, a wide range of acceptors were employed and afforded good yields. In the case of *iso*-propanol a yield of 97% was observed. The 1-*O*-

*iso*propylmannoside was identified by the presence of two 3H doublets at 0.98 and 1.1 ppm, both with coupling constants of 6 Hz corresponding to the two methyl groups of the *iso*-propanol fragment in different geometrical environments. The presence of an α-anomeric signal at 4.86 ppm is also indicative of the product. Finally HRMS gave a molecular ion of 600.3318 Da ($M+NH_4$) which corresponds with the literature. For the case where benzyl alcohol was used as the acceptor a yield of 97% was observed. An expected increase in value of the integral observed for the benzyl protons in the 1H-NMR spectrum when compared to that of the α-anomeric signal at 4.9 ppm and $J^{1,2}$ coupling constant of 2Hz integrates to a 25:1 ratio. HRMS also identifies the presence of the molecular ion of 648.3324 ($M+NH_4$) Da corresponding to data published for this compound.[194]

In the case where glycosylation was performed with pentenyl alcohol a 98% yield of the 1-*O*-pentenylmannoside was observed after column chromatography. The pentenyl glycoside was identified by the presence of a 1H multiplet between 5.62 and 5.83 ppm for the vinyl proton comprising of coupling to the *cis* terminal vinyl proton, a *trans* coupling to the second terminal vinyl proton and that to the protons on the adjacent methylene group. Also present was the α-anomeric signal at 4.66 ppm with coupling constant of 2 Hz and the sp^3 protons of the alkyl chain which appear as a series of multiplets between 1.0 and 2.2 ppm. HRMS also indicated the presence of a molecular ion at 626.3481 Da ($M+NH_4$). In the case of the secondary acceptor cyclohexanol a yield of 92% was observed. The ^1H NMR spectrum identified the cyclohexane ring as a 10H multiplet between 1.04 and 1.77 ppm along with a 1H α-anomeric signal at 4.92 ppm with coupling constant of 2Hz. HRMS again identified the molecular ion of 640.3642 Da (M+NH4). When *N*-carbobenzyloxy-L-threonine methyl ester was employed a yield of 72% of the 1-*O*-

N-carbobenzyloxy-L-threonine methyl ester mannopyranoside was observed and identified by an α-anomeric doublet at 4.75 ppm with coupling constant of 2 Hz indicative of an α-anomer. Also observed was an increase in number of benzyl protons when the integral height in the aromatic region in the spectrum of product is compared with that of the integral height of the anomeric proton. The presence of methyl ester protons of the acceptor fragment are observed at 3.49 ppm. HRMS also identified the presence of the molecular ion being ($M+NH_4$) 789.3515 Da. Interestingly in this case it was possible to obtain crystals of this *O*-glycoside which allowed us to demonstrate the anomeric configuration of the glycosidic bond which confirmed the presence of an α-linkage (Figure 22 and Figure 23).

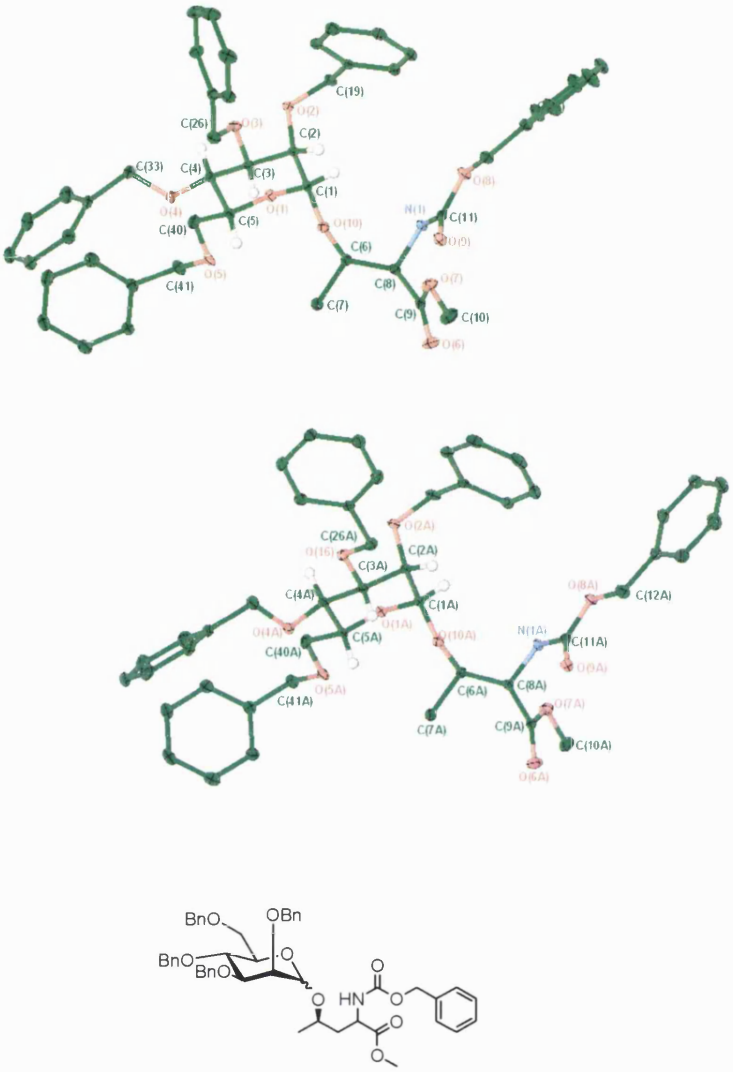


Figure 22: *Crystal structure for* 1-*O*- *N*-carbobenzyloxy-L-threonine *derivative*

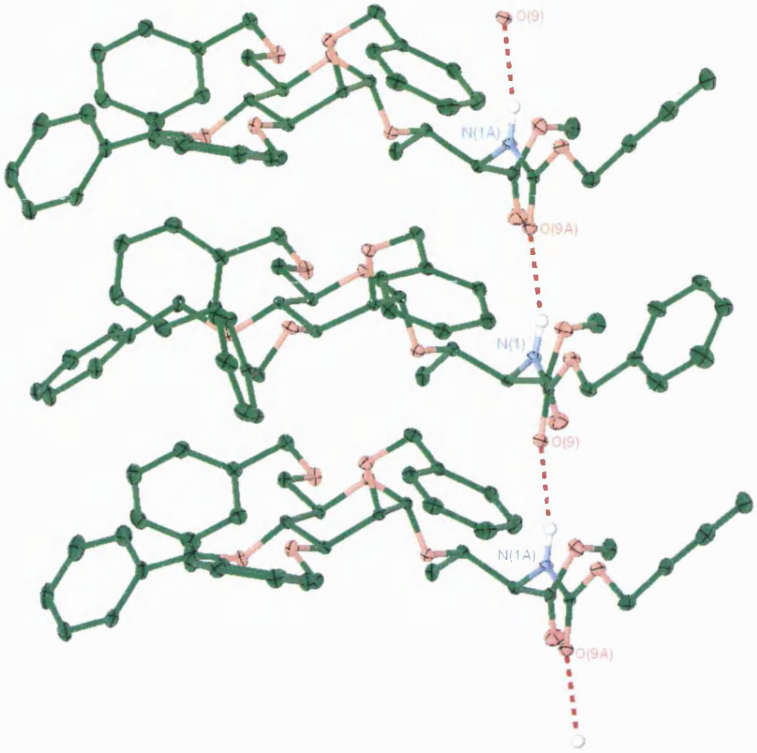


Figure 23: *Crystal structure showing 'Stacking'*

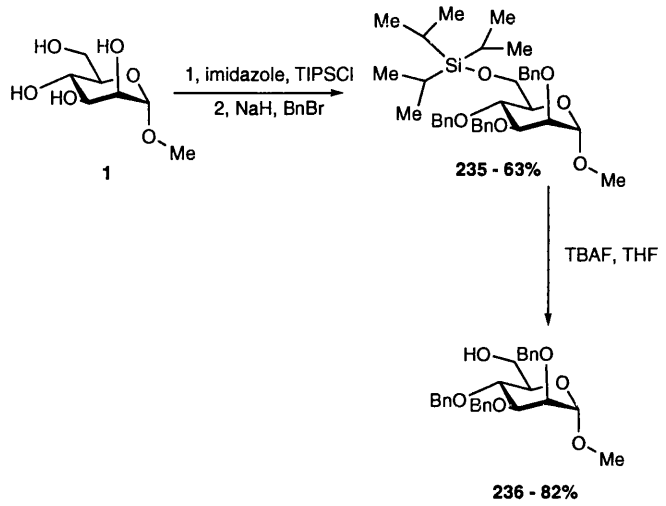
Figure 22 and Figure 23 show the pyranose ring in a $^4C_1$ conformation as an α-anomer. Interestingly it is also observed that there is Hydrogen bonding interaction between the amide hydrogen and the carbonyl oxygen of the benzyl ester of a second molecule of this glycoside. The stereochemical outcome of the reactions was a little disappointing; however we were able to investigate this reaction further attempting to alter the stereochemical outcome. Firstly, because separation of the β-anomer of glycosyl donor **259** was possible it was decided to investigate reactivity and stereochemical outcome of reactions using β-**259** as the glycosyl donor. Unfortunately, the stereochemical outcome here was the same as the experiment where the α-anomer was used as the glycosyl donor and again in all cases the α-*O*-glycosides were observed. On a positive note the timescale for these reactions was

short making the use of this donor system practical in addition to the fact that the yield when simple acceptors were used was high being > 90%.

Another acceptor was β-dihydrocholestanol, which also gave a good glycosylation yield of 85%. ^{1}H-NMR gave an anomeric signal as a doublet at 4.96 ppm with the usual 2 Hz coupling constant and cholesterol signals between 0.48 and 1.97 ppm. The molecular ion for this compound was also found by HRMS 928.6428 Da ($M+NH_4$).

Investigations using glycoside based acceptors were also attempted on pyridyl donors **α-259** and **β-259** (Table 15 and Table 16) to demonstrate the true utility of this process. Initially two acetal protected sugar based glycosyl acceptors were employed. The first was a secondary acceptor with a C-3 unprotected alcohol based on glucose and the second was a primary C-6 unprotected alcohol acceptor based on galactose. Also investigated was a primary C-6 tri-benzylated glycosyl acceptor **265** based on mannose and a secondary C-4 unprotected acceptor **269** based on glucose, the latter two had to be prepared. Acceptor **265** was prepared by reaction of **1** with 1.1 equivalents of triisopropylsilyl chloride and 2.2 equivalents of imidazole in DMF. The intermediate silylated product was then benzyl protected using benzyl bromide and sodium hydride in DMF to give C-6 silyated glycoside **264** in a 63% yield identified by the presence of a 18 hydrogen multiplet at 1.2 ppm and HRMS of 638.3881 Da ($M+NH_4$). Subsequent removal of the TIPS protecting group was achieved by the addition of TBAF to silylated glycoside **265** in DCM at 0 °C gave C-6 unprotected alcohol **265** in good yield 82% (Scheme 67). This was identified by the presence of a 1H broad singlet at 2.1 ppm and alcohol stretch in the IR spectrum of 3471 cm^{-1}. Subsequent use of these acceptors in glycosylation reactions resulted in disappointing yields. The limited amounts of each disaccharide produced for the C-6

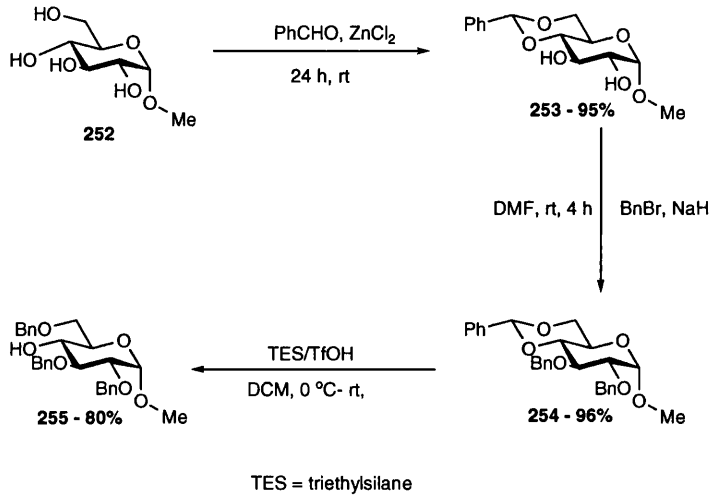
galactose and the C-6 mannose acceptors made identification inconclusive and thus their full analysis is not mentioned in this thesis. For the case of the C-3 unprotected glucose furanoside acceptor ^{1}H-NMR analysis is quoted only. Optimisation of these reactions was not improved by increasing the reaction time to 24 hours and in fact LRMS showed the absence of the desired molecular ion.



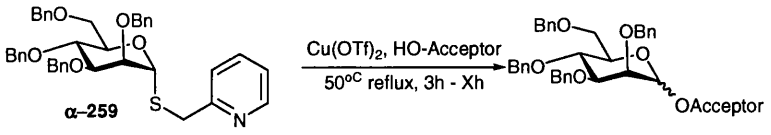
Scheme 67: *Preparation of C-6 mannose acceptor* **265**

Synthesis of the C-4 unprotected alcohol **269** was achieved by firstly protecting the hydroxyl groups at C-6 and C-4 as a benzylidene acetal to give glycoside **267** (Scheme 68). A substantial stock of this compound was kindly donated to us courtesy of Professor Grant Buchannan. There are several of methods for the selective generation of a C-4 unprotected glycoside namely the addition of sodium cyanoborohydride with hydrochloric acid in THF to a C-4 – C-6 benzyilidene acetal.[3] An alternative method has been developed by Dinino and co-workers,[195] in which the choice of reducing agent allowed the selective generation of 6-*O*-benzyl-4-hydroxy derivatives by the use of triethylsilane (TES) and trifluoroacetic acid (TFA). This was the method employed to generate the target glycoside **269.** Thus, the addition of the TES/TFA system to the benzylated benzylidene **268** in DCM (Scheme 68) was analysed. This generated the 4-hydroxy derivative **269** in good yield (96 %)

identified by the presence of a 3H singlet at 3.43 ppm and 15H multiplet between 7.28 and 7.58 ppm indicating the presence of benzyl protons and the dissappearence of the C-H singlet of the acetal at 5.78 ppm and the lack of chemical shift change in the range of 0.33 ppm where a C-6 benzyl protected *versus* a C-6 unprotected glycoside, was not seen in this case. The α-anomeric signal was found at 4.48 ppm as a doublet with coupling constant of 2 Hz and alcohol stretch was indicated by the presence of a broad OH stretch at 3051.6 cm^{-1}.



Scheme 68: *Preparation of C-4 hydroxy derivative* **269**



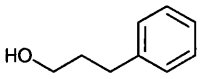
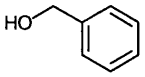
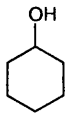
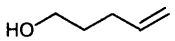
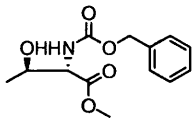
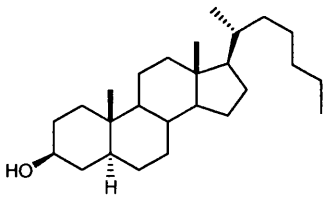
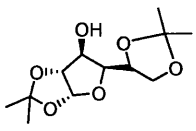
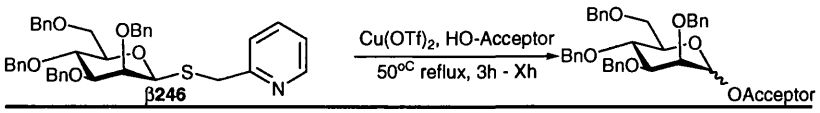
Glycoside	Acceptor	Yield
α-259		85 (100% α)
α-259		97 (100% α)
α-259		96 (100% α)
α-259		97 (100% α)
α-259		92 (100% α)
α-259		98 (100% α)
α-259		72 (100% α)
α-259		87 (100% α)
α-259		12 (100% α)[a]

Table 15: *Glycosyl acceptor study for α-259*

[a]Based on preliminary ^{1}H NMR analysis



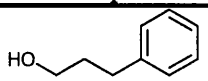
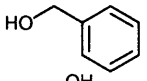
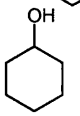
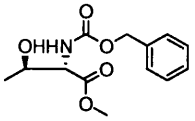
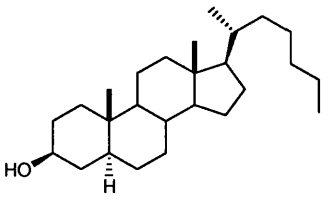
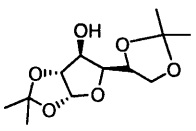
Glycoside	Acceptor	Yield*
β-259		85 (100% α)
β-259		97 (100% α)
β-259		96 (100% α)
β-259		97 (100% α)
β-259		92 (100% α)
β-259		98 (100% α)
β-259		71 (100% α)
β-259		78 (100% α)
β-259		16[a] (0) (100% α)

Table 16: *Glycosyl acceptor study for α-259*

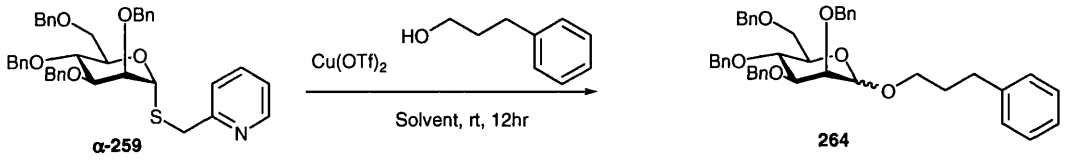
[a]Based on preliminary ^{1}H NMR analysis

2.6 Effect of solvent on glycosylation of thioglycoside donor **259**

As described in the introduction of this thesis the solvent used in a particular glycosylation can dramatically affect not only the yield of a given reaction but also the stereochemical outcome of that reaction. Thus with our pyridyl thioglycoside **259** in mind it seemed prudent to investigate this glycosyl donor's reactivity or in a selection of common organic solvents. The organic solvents were chosen based on their varying properties. Initially five solvents were chosen, acetonitrile was chosen due to its properties as a participating solvent in glycosylation reactions. Toluene was chosen because of its solubility compatibilities towards highly aromatic systems. Dichloroethane (DCE) was chosen because of its decreased volatility when compared to DCM and tetrahydrofuran was chosen due to its ability to coordinate.

The typical procedure mirrored that of the previous optimized conditions for glycosylation reactions performed in DCM where 2.2 equivalents of 3-phenylpropanol and 1.1 equivalents of copper(II) triflate were used and reactions were performed at a 50 °C reflux.

Results for glycosylations performed on glycosyl donor **259** are shown in Table 17. Yields in all cases were lower than that found for the use of DCM although good yields resulted when acetonitrile, toluene and DCE were used as the reaction solvent. In all cases again the production of the α anomer of **264** was dominant as indicated by the presence of a doublet at 4.77 ppm with coupling constant of 2 Hz and C-1 carbon signal at 98.3 ppm. This further suggests the dominance towards a more S_N1 type mechanism whereby formation of the α anomer of *O*-glycoside is driven by the stabilizing anomeric effect.

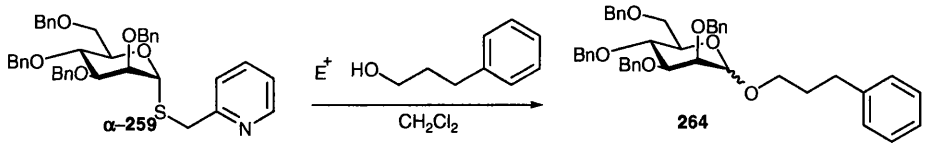


Glycoside	Solvent	Yield*
α-259	ACN	76 (100% α)
α-259	DCM	67 (100% α)
α-259	DCE	62 (100% α)
α-259	Toluene	37 (100% α)

Table 17: *Solvent study for α-259*

2.7 Glycosylation via electrophilic activation of pyridyl thioglycoside donor **259**

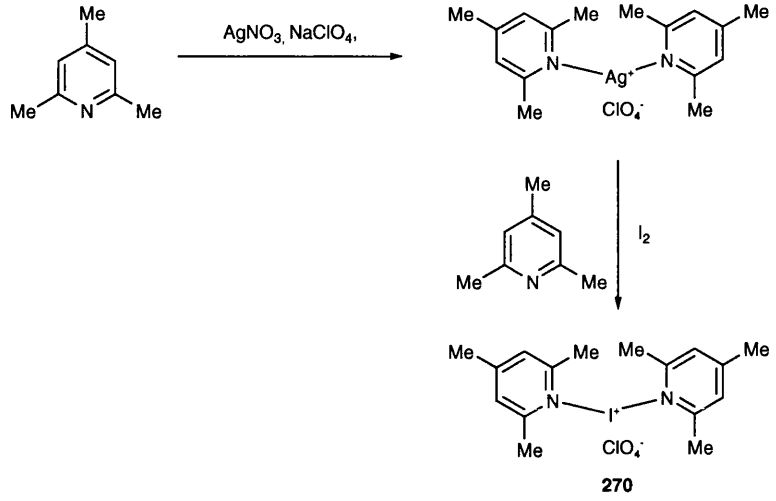
Classically it has been demonstrated that activation of thioglycosides is possible by electrophilic species as described earlier. Commonly, activation of thioglycosides has been achieved using the following electrophilic species: iodonium dicollidine perchlorate (IDCP), dimethyl (methylthio) sulfonium triflate DMTST,[196-198] TMSOTf, [166] MeOTf,[199] NIS/TfOH,[165] I_2[170] and NIS/AgOTf[200] all of which have been known to invoke good to excellent glycosylation of thioglycoside donors in general, the results of which are shown in Table 18. In order to evaluate our new system we decided to perform glycosylations based on known electrophilic activation strategies.



Glycoside	Activator	Equiv	Temp (°C)	Time (h)	Yield	α/β
α-259	NIS/TMSOTf	1.1/10mol%	-78	5 mins	42	100%α
α-259	NIS/TMSOTf	1.1/10mol%	-20	5 mins	30	100%α
α-259	NIS/TMSOTf	1.1/10mol%	-20-Rt	12	84	100%α
α-259	NIS/AgOTf	1.1/1.1	Rt	3	55	100%α
α-259	NIS/TfOH	1.1/10mol%	-78	5 mins	35	100%α
α-259	MeOTf	1.1	Rt	3	44	100%α
α-259	DMTST	1.1	Rt	3	37	100%α
α-259	I_2	1.1(2.2)	Rt	3	30 (26)	100%α
α-259	IDCP	1.1(2.2)	Rt	3	27 (37)	100%α

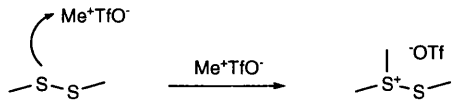
Table 18: *Electrophilic activation study*

Central to this study was the synthesis of activator systems of IDCP and DMTST. IDCP was synthesised in a 2 step synthesis from the reaction between di-*sym*-collidine, silver perchlorate, and silver nitrate forming the silver di-*sym*-collidine perchlorate intermediate which is subsequently reacted with iodine to form the iodonium perchlorate complex (Scheme 69). [201] DMTST **270** is synthesised by the reaction between dimethyl sulfide and methyl triflate in dichloromethane devised by Tillet and co-workers (Scheme 70). [202]



Scheme 69: *Preparation of IDCP*

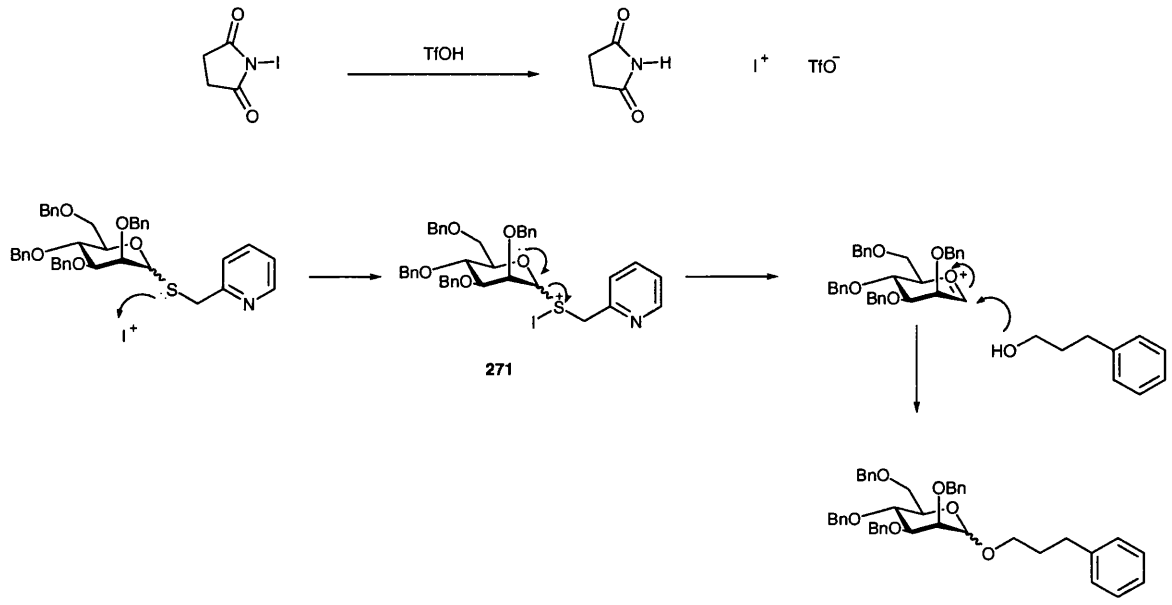
The results shown in Table 17 show that for this system the yields do not compare favourably with those generally achieved for commonly used thioglycosides. In all cases there was unidentifiable baseline material observed in TLC analysis. In the cases where NIS and TMSOTf were used to generate catalytic iodide, two spots were seen by TLC close together around the R_f of that for the know α-anomer as identified by Lewis acid mediated studies. This presumably is due to the generation of both anomers of product but on quenching of the reaction mixture only the α-anomer was identified by ^{1}H-NMR analysis. Attempts to synthesise the β-anomer by use of low reaction temperatures proved unsuccessful with only α-glycoside synthesis resulting in each case.



Scheme 70: *Preparation of DMTST*

Possible explanations towards the low reactivity of the pyridyl thioglycoside **259** could lie in the reactivity of pyridines towards electrophilic reagents or the decreased reactivity of the sulfur due to the electron donating properties of the pyridine nitrogen. The reaction mechanism for the NIS mediated glycosylations are said to

proceed *via* the catalytic generation of iodonium cation which acts as the active electrophile in this process. Addition of the electrophile proceeds *via* the lone pair of electrons present on the sulfur atom of the thioether generating the corresponding thiazonium cation **258** and hence the active leaving group. Formation of the usual oxonium ion proceeds, followed by attack of the glycosyl acceptor to give the corresponding *O*-glycoside (Scheme 71) in the cases highlighted in Table 18.



Scheme 71: *Proposed electrophilic activation of* ***259***

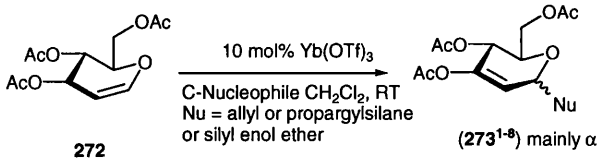
2.8 *C*-glycoside synthesis

2.8.1 Recent methods for the synthesis of *C*-glycosides[203-206]

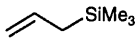
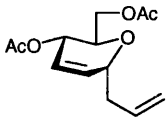
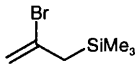
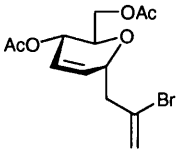
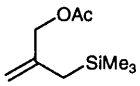
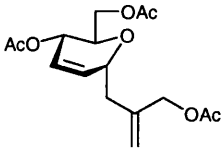
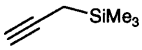
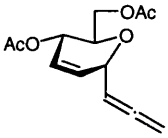
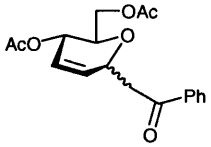
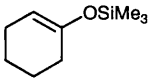
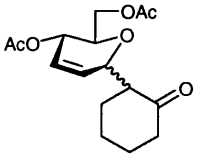
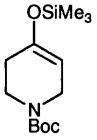
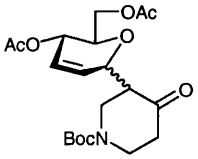
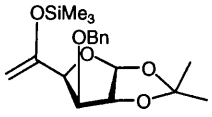
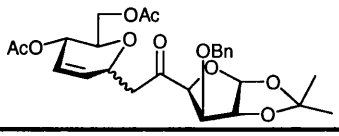
The synthesis of *C*-glycosides[207] has over recent years been subject to intensive study for numerous reasons: (1) The synthesis of naturally occurring *C*-nucleosides with pharmacological properties[208] has led to an increase in requirement to produce biologically active synthetic analogues; (2) There are several key macromolecules such as palytoxin,[209] spongistatin[210] and halichondrin [211] which all require *C*-glycosides as chiral building blocks; (3) *C*-glycosides have been shown to exhibit enzyme inhibition properties for carbohydrate processing enzymes and are stable analogues to glycans involved in intra- and intercellular processes.[212]

To this time there are few synthetic methods for the general production of *C*-glycosides, indeed *C*-glycosylation *via* traditional glycosyl donor types is rare with the exception of glycosyl fluorides **6**,[213] glycosyl acetates.[214] Most other types of glycosyl donor have either shown no reactivity or have not been published as of yet. Most common routes to the synthesis of *C*-glycosides involve the use of glycals **272** (Scheme 72). Commonly, though, reaction of these systems are troublesome with glycosylation proceeding predominantly with only strong Lewis acids like $BF_3{\cdot}OEt_2$,[215,216] $TiCl_4$[217] and TMSOTf.[218] Other reagents include DDQ,[219] $InCl_3$,[220] $AlCl_3$.[218] Many of these methods suffer not only in terms of yields but stereoselectivities, reaction temperatures and compatibilities with other functionalities present within the glycosides used.

Schmidt and co-workers[221] have demonstrated the use of tri-*O*-acetyl glucal with a variety of silylated species as acceptors with the reaction being catalysed with 10 mol% of $Yb(OTf)_3$ (Scheme 72). Their results where not only high yielding but also highly selective for the corresponding α-*C*-pseudo-glycals, these results are shown in Table 19.



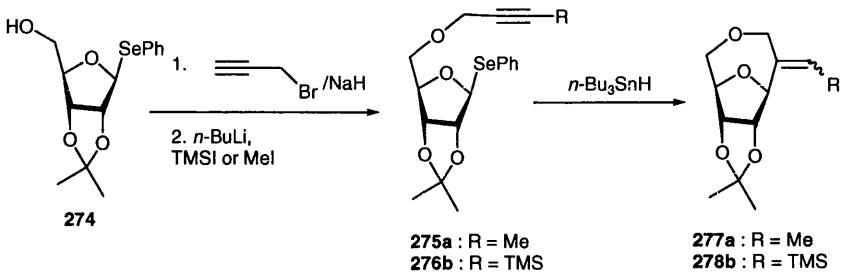
Scheme 72

Entry	Acceptor	Glycoside	Time (h)	Yield (%) [a]	α/β [b]
1			3	94	α
2			4	89	α
3			4	89	α
4			16	92	α
5			10	90	8:1
6			12	89	11:1
7			15	84	8:1
8			12	88	5:1

(a) Isolated yields after column chromatography. (b) α/β ratios were determined by ^{1}H-NMR (250 MHz)

Table 19. *Glycosylation of 259 with silylated nucleophiles in the presence of 10 mol% Yb(OTf)$_3$*

Kim and co-workers[222] have developed a novel route to *C*-glycosides; in their approach they employ phenylselenofuranosides to perform selective, high yielding *C*-glycoslations employing a radical based cyclisation (Scheme 73).



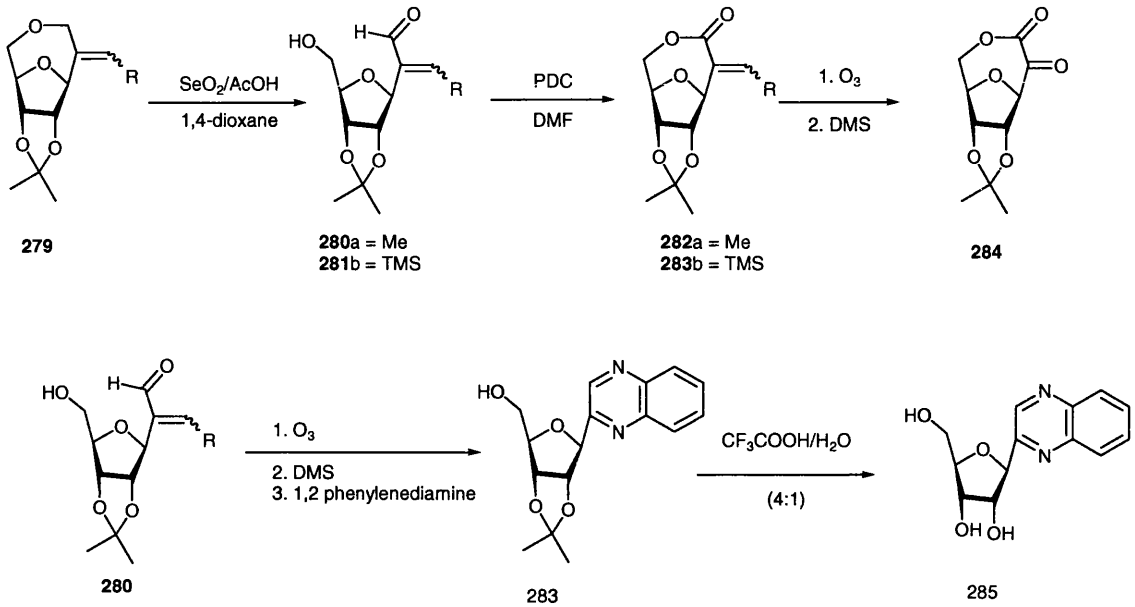
Scheme 73: *C-glycoside synthesis*

Firstly alkyne intermediates **275-278** are produced by a two step process involving treatment of **274** with propargyl bromide/NaH then subsequent deprotonation of the alkyne with *n*-Buli and addition of electrophiles MeI and TMSI. Generation of radical species occurs in the usual way by treatment of intermediates **275-276** with Bu_3SnH/AIBN in toluene at 80 °C, which gave cyclisation products **277** and **278** in 93 % and 82% yield for **275** and **276** respectively. The presence of the methyl and trimethylsilyl substituents proved essential in this process due to competing hydrostannation of the triple bond.

Kim and co-workers then proceeded to perform allylic oxidation of **279** with SeO_2 in dioxane in the presence of acetic acid to give the corresponding vinyl aldehyde (**280** and **281**) (29% for Me **280** 69% for TMS **281**) *via* hemiacetal intermediate (Scheme 74). Treatment of **280** and **281** with pyridinium dichromate in DMF gave lactones **283** and **284** in 30 % and 74 % respectively also through hemiacetal intermediates, which in turn could be converted to **285** in 19% yield, which is a precursor in the synthesis of showdomycin [223]through ozonolysis and reductive cleavage.

Synthesis of pyrazine *C*-glycoside **280** was achieved by ozonolysis and subsequent reductive cleavage on aldehydes **280 & 282** to yield α-keto aldehyde intermediate

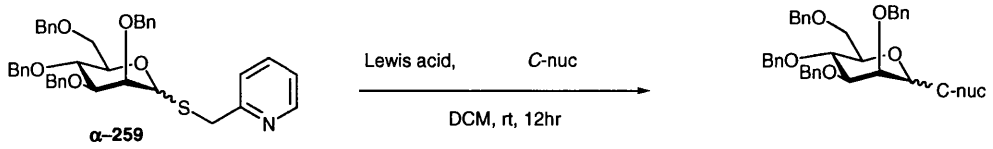
which was reacted with 1,2-phenylenediamine without purification. Compound **282** was obtained in a 21% yield. Deprotection of **282** was achieved by treatment with CF_3COOH and H_2O which gave **283** in a 44% yield (Scheme 74)



Scheme 74: *C-glycoside synthesis*

2.8.2 The use of pyridyl thioglycoside donor 259 towards the synthesis of *C*-glycosides

During the course of our investigations it became clear that there are relatively few synthetic protocols for the direct synthesis of *C*-glycosides from traditional donors. The reactivity of our system towards the simple acceptors outlined thus far encouraged us to investigate our system's capability towards the synthesis of *C*-glycosides using common carbon nucleophiles. Initially conditions mimicking those employed in the Lewis acid mediated study described earlier were employed. Hence to thioglycoside **α-259** in DCM was added 1.1 equivalents of copper(II) triflate and 1.5 equivalents of the carbon nucleophiles, results are shown in Table 20, initially the reactions were performed over 3 hours although this was extended to 24 hours in order to attempt to increase the yield of these reactions (Table 20).



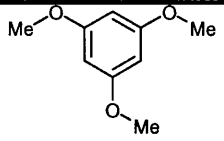
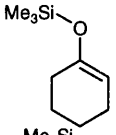
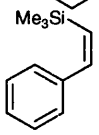
Glycoside	Acceptor	Time	Yield
α-259		3(24)	0(0)
α-259		3(24)	0(0)
α-259		3(24)	0(0)
α-259		3(24)	0(0)
α-259		3(24)	0(0)

Table 20: *C-glycosylation study of α-259*

Unfortunately as can be seen in each case there was no identified *C*-glycoside product observed. For the most part low resolution mass spec (LRMS) resulted in observed ions indicative of the initial starting thioglycoside but the allyl *C*-nucleophiles, however, gave complex mixtures by LRMS giving ion peaks at 580 Da ($M+NH_4$) for the allyl trimethyl tin variant and 630 Da ($M+NH_4$) for the tertiary butyl tin reagent in both cases these ion peaks are unidentifiable.

2.9 Conclusions and Future Work

During the course of this study it has become apparent that the scope of modern day sugar chemistry is immense, being arguably the most studied and published area of synthetic organic chemistry. Thus far it may be concluded that the initial series of thioglycosides show significant reactivity differences towards a variety of different Lewis acids with notable examples being the use of copper(II) triflate with both pyridyl **259** and furfuryl **260** thioglycosides and scandium(III) triflate and hafnium(IV) triflates showing a preference for the thiophene based thioglycoside in the limited reaction time in which these trial reactions were carried out. As a result of this there are avenues to explore for novel chemoselective approaches. Also discovered from the experiment where triflic acid was used as the activator, was the fact that the metal Lewis acid dictates whether glycosylation takes place rather than activation *via* the *in-situ* generation of triflic acid in these glycosylations. For this experiment similar conditions were used as for the optimised copper(II)triflate experiments but with the substitution of 1.1 equivalents of triflic acid. The result of which was that no glycosylated product was observed by TLC or by crude NMR.

In the case of pyridyl thioglycoside **259** good yields (> 90%) have been seen when simple glycosyl acceptors have been employed. The expected reduction in reactivity which is typically seen when 'metal' based Lewis acids have been employed, has been observed when sugar acceptors have been employed.[224] Preliminary analysis of the ^{1}H-NMR spectra for the diacetone-D-glucose, diacetone-D-galactose and **265** glycosyl acceptors indicates the presence of disaccharide product, however the use of other NMR techniques proved inconclusive for these examples These reactions where repeated and reaction times were increased to 24 hours, an increase in yield was not seen in fact the reactions failed with only glycosyl donor **259** being

identified in the reaction mixture by LRMS. Thus, the first line of investigation is further optimisation of the reactivity of the pyridyl thioglycoside towards sugar based acceptors by an additional increase in reflux temperature.

Unfortunately generation of the initial series of thioglycosides was severely hampered by the complexity of producing sufficient quantities of pyridyl and thiophenyl mercaptans for our key initial study and it was not until both mercaptans became commercially available that significant progress was made. For the continuation of our work, competition experiments have been devised to demonstrate the feasibility of using our novel glycosyl donors in a competitive one pot strategy. These will not only compare the differing reactivity of the glycosyl donors developed by ourselves but also some of those that are in use by modern day sugar chemists. For example the benzyl thioether thioglycoside showed no reactivity towards copper(II) triflate, thus inferring that this will also be true for the ethylthioglycoside analogue. Also commonly know phenylseleno glycosyl donors which are used in glycoside synthesis and are activated by both NIS and NBS mediated strategies could be inserted into the reactivity order and hence provide further activation levels. Thus if these systems fail to react with the copper (II) and/or erbium (III) triflates then this could allow for a one pot strategy involving the potential for selective activation of the pyridyl, furfuryl, thiophenyl, benzyl thio, ethylthio and phenylseleno glycosides which could result in the generation of target hexasaccharides. The strategy would involve the generation of a series of 6-hydroxy donors (Figure 24) which would each posses the different heteroaromatic leaving groups along with the more traditional leaving groups mentioned. These 6-hydroxy donors would then be sequentially glycosylated to the initial pyridyl thioglycoside donor **259** (Scheme 76) using the copper methodology. This would then generate a disaccharide donor possessing the

furfurylthio leaving group which could then be used in a second glycosylation step by subsequent addition of copper(II) triflate and the addition of 6-hydroxy thiophene acceptor **289** to generate a trisaccharide **291** based purely on our novel glycosides, with the use of the 6-hydroxy phenyl thioglycoside. Subsequent glycosylation then activation protocols using the known methodologies and routinely used glycosyl donors as previously mentioned would allow for the generation of target pentasaccharide **293**. Further down the line would be the development of hexasaccharides with other linkage patterns i.e. Man(1-4)Man, Man(1-3)Man.

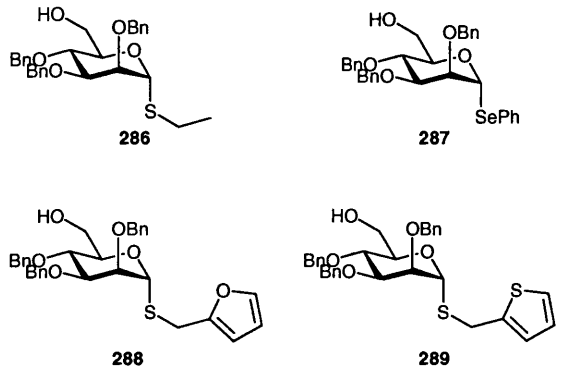
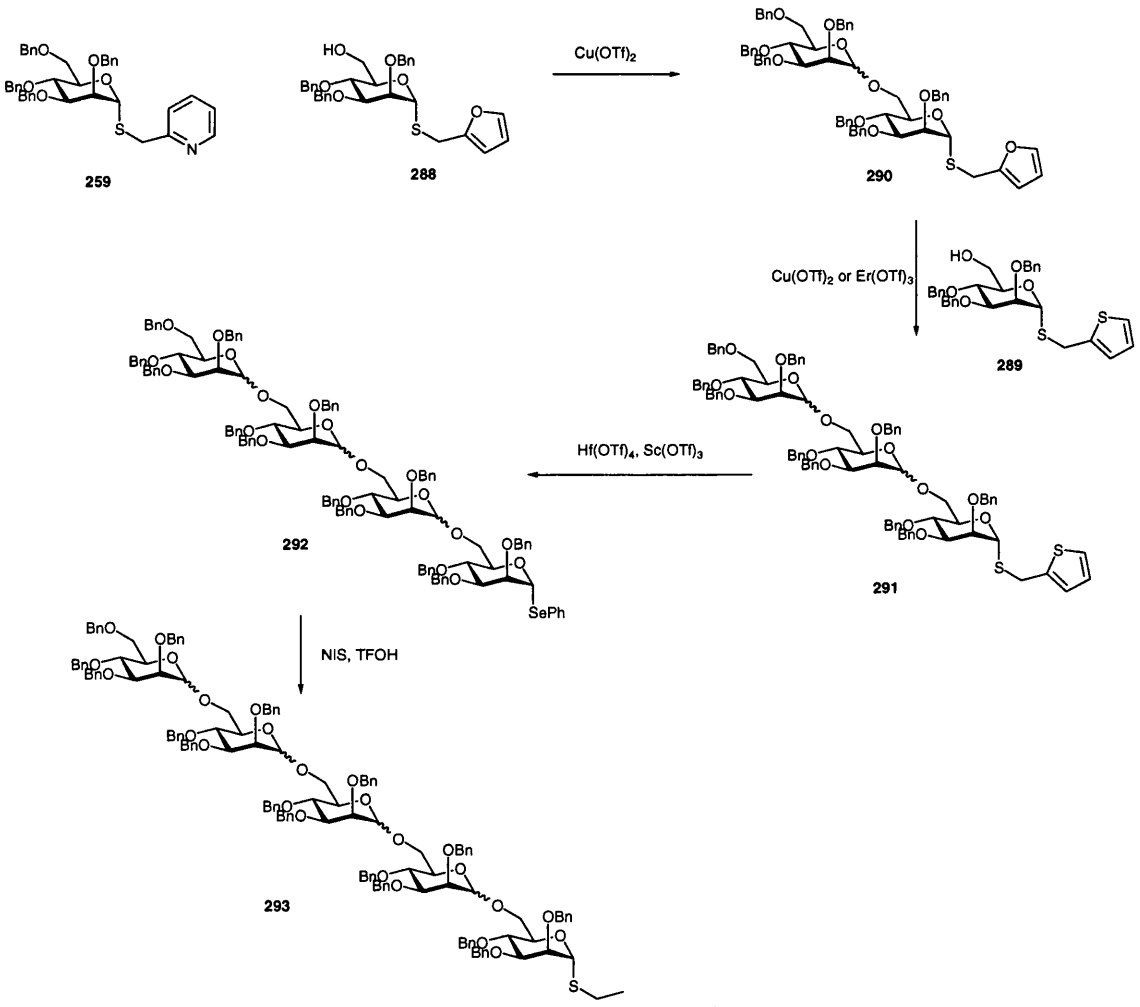


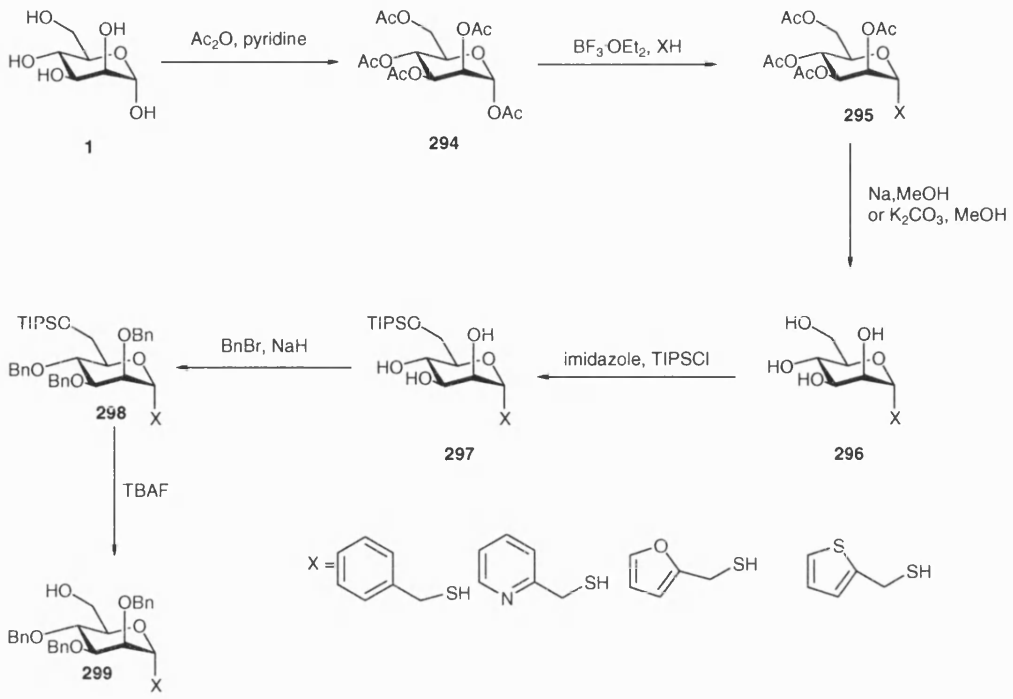
Figure 24: *Novel chemoselective acceptor glycosides*

This strategy was has been initiated with the synthesis of the key mannose pentaacetate donor **294**. Although this compound is commercially available its synthesis was achieved directly from D-mannose by the addition of acetic anhydride with pyridine as the required base and DMF as the reaction solvent, which resulted in a 95% yield of the expected pentaacetate **294**. From this it was possible to produce the appropriate glycosyl donors namely the ethyl thio, furfury methyl, and thienyl methyl thioglycosides and the phenyl selenoglycoside in accordance to the protocol utilized by Osborn and co-workers.[197] Each of these glycosides were accessed in reasonable yield and identified by ^{1}H and ^{13}C NMR spectroscopy. From here deprotection and subsequent protection of the C-6 hydroxyl as the TIPS silyl ether then subsequent benzylation was attempted. Unfortunately the fully benzylated

products were not prepared in these reactions. As a result of time constraints further attempts at producing the appropriate C-6 silyl ethers **298** were not attempted. However starting points for the next researcher in this strategy are evident, firstly a more sequential strategy should be attempted in which each intermediate is identified and instead of deprotection of the corresponding tetraacetate with sodium methoxide perhaps the use of potassium carbonate in methanol would be a milder deprotection protocol.

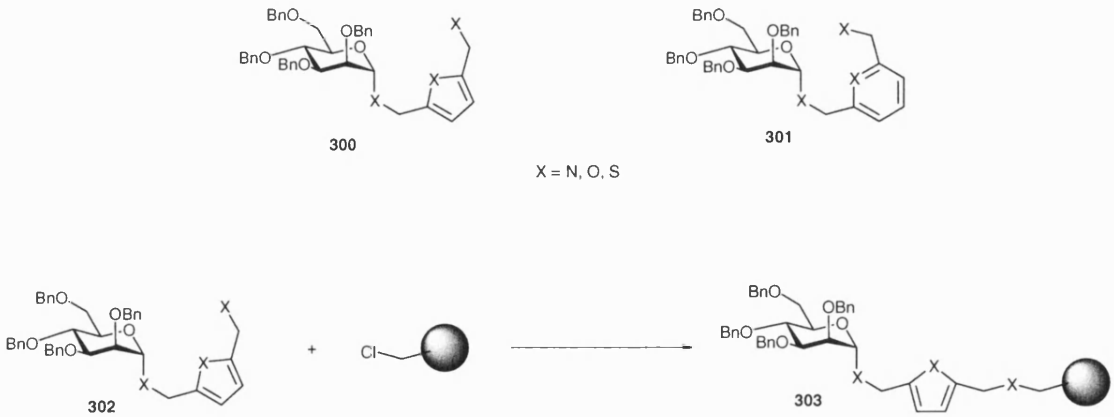


Scheme 75: *Target pentasaccharide synthesis*



Scheme 76: *Synthetic route for novel C-6 acceptors*

Future development of our chemoselective donors would also include the possible tridentate properties seen in glycosides **300 –301** Scheme 77. Again there is a possibility of additional chemoselectivity in such donors with the additional property that the presence of functionality at positions either side of the heteroatom of the heterocycles would allow the possibility for the development of these systems towards polymer supported glycosylation (Scheme 77).



Scheme 77: *Novel polymer supported glycosides*

Chapter 3

3 Experimental

3.1 General Experimental Procedures :

Commercially available solvents and reagents were obtained from the following distributors; Sigma-Aldrich, Lancaster Synthesis and Fischer Scientific and unless stated were used without further purification. Dichloromethane, acetonitrile and *N,N*-dimethylformamide were distilled from calcium hydride and stored under nitrogen over 4Å molecular sieves. 'Petrol' refers to the fraction of petroleum ether boiling in the range of 40-60°C.

Analytical thin layer chromatography was performed on precoated glass, plastic and aluminium backed silica gel (Merck Kieselgel 60 F_{254}) plates. The plates were visualized by ultra-violet light (at 254 nm) and by staining with either vanillin, potassium permanganate, iodine on silica or combinations of the above. Column chromatography was performed using Merck Kieselgel 60H silica gel.

All melting point were obtained with a Büchi 535 instrument and are uncorrected. Infra red spectra were measured in the range of 4000-600cm^{-1} using a Perkin-Elmer 1600 series FT-IR spectrophotometer, with internal calibration. Elemental analysis was carried out using a Carlo Erba 1106 elemental analyzer or an Exeter Analytical Inc CE-440 Elemental analyzer.

Mass spectrometry was performed at the EPSRC National mass spectrometry service Swansea. Low resolution EI and CI were performed on a Quattro II triple quadrupole instrument. Low resolution FAB was performed on their autospec system. Accurate mass experiments were carried out with a MAT900 instrument. Low resolution electrospray was carried out on the Quattro II and MAT900 systems and accurate mass again was performed on the MAT900 instrument.

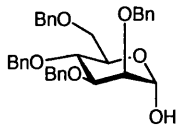
^{1}H, ^{13}C nuclear magnetic resonance spectra were recorded on either a Varian EX-400 (400 MHz) or a Bruker 300 (300 MHz) spectrometer. Chemical shifts (δ) are expressed in parts per million (ppm), and are relative to an internal reference of residual protic solvent. The multiplicities of the observed signals are presented in the following manner: singlet (s), broad singlet (brs), doublet (d), doublet of doublets (dd), double doublet of doublets (ddd), triplet (t), triplet of doublets (td), quartet (q), or multiplet (m). All coupling constants (J) are expressed in Hertz (Hz).

Where possible specific assignments of protons and carbons were achieved using 2-D spectroscopy, protons being assigned by ^{1}H-^{1}H COSY spectroscopy and carbons via ^{1}H-^{13} HETCOR spectroscopy.

Single crystal X-ray diffraction data was collected on a Nonius Kappa CCD machine. Structure determination and refinement were achieved using SHELX suite of programs; drawings were produced using ORTEP software.

3.2 Specific experimental procedures

Preparation of 2,3,4,6-tetra-*O*-benzyl-α-D-mannose 256[225]

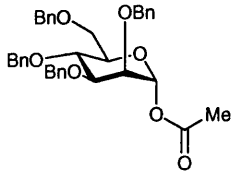


Method 1

Sodium hydride [40% w/w dispersion in mineral oil] (7.58 g, 7 equiv) was added over a 2 hour time period to a solution of methyl-α-D-mannopyranoside (5.25 g, 9.73 mmol, 1 equiv) in benzyl chloride (131 mL, 25 equiv). The solution was then heated under reflux for 1.5 hrs or until the solution turned yellow and solidified. The solution was then cooled to room temperature and extracted with water (2 × 150 mL) to remove all soluble organic material. The organic layer was then concentrated *in-vacuo* and distilled under vacuum to remove the excess benzyl chloride. The orange syrup thus produced was then dissolved in acetic acid (250 mL) and a solution of 3M H_2SO_4 (30 mL) was added. The reaction was stirred under reflux for 1h. The crude mixture was then extracted with ethyl acetate (2 × 100 mL). The organic extract was then neutralized with sodium hydrogen carbonate solution, dried ($MgSO_4$), filtered and the ethyl acetate removed under vacuum. Following column chromatography on silica (9:1 petrol/ethyl acetate), the free hydroxy mannose derivative **256** was obtained (12.30 g, 85% yield) as a viscous orange oil R_f = 0.72 (7:3 petrol/ethyl acetate). Data obtained was in agreement with that found in the literature. ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 3.65-3.79 (3H, m, **H-2**, **H-3**, **H-5**), 3.81 (2H, dd, *J* = 9, 3, H6, H6'), 4.07 (1H, app.t, *J* = 9., 10, **H-4**), 4.51-4.57 (4H, m, Ph**CH**$_2$O), 4.61-4.80 (3H, m, Ph**CH**$_2$O), 4.89 (1H, d, *J* = 11, Ph**CH**$_2$O), 5.22 (1H, d, *J* = 1.9, **H-1**), 7.15-7.41(20H, m, Ar-**H**). ^{13}C-NMR (75.4 MHz, $CDCl_3$), δ = 69.2 (Ph**C**H$_2$O), 72.3

(PhCH$_2$O), 72.7 (PhCH$_2$O), 73.6 (PhCH$_2$O), 73.8 (C-2), 74.8 (C-3), 74.7 (C-4), 75.5 (C-6), 79.5 (C-5), 91.6 (C-1), 128.1(Ar **C**-H), 128.3(Ar **C**-H), 128.4(Ar **C**-H), 128.5 (2 × Ar **C**-H), 128.6 (Ar **C**-H), 128.7 (2 × Ar **C**-H), 129.3 (Ar **C**-H), 138.5 (Ar **C**), 138.6 (Ar **C**), 138.7 (Ar **C**). IR(liquid film) vmax (cm^{-1}) = 3413.2, 3029.9, 2919.0, 1953.2, 1875.2, 1810.7, 1742.1, 1585.4. HRMS (M+NH$_4$) calcd for $C_{36}H_{42}NO_7$ expected 558.2512 found 558.2597

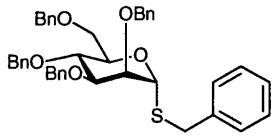
Preparation of 2,3,4,6-tetra-*O*-benzyl-1-acetyl-α-D-mannose 257[226]



2,3,4,6-Tetra-O-benzyl-α-D-mannose 243 (8.22 g, 15.2 mmol, 1 equiv) was dissolved in dry DCM (20 mL). To this solution was added pyridine (2.7 mL, 33.1 mmol 2.2 equiv) and acetyl chloride (1.2 mL, 16.8 mmol 1.1 equiv). The reaction was stirred at 0 °C and allowed to warm slowly to room temperature. The reaction was monitored by TLC until the reaction had reached completion. The reaction mixture was then extracted with saturated copper (II) sulfate solution (3 × 50 mL) to remove the excess pyridine, and then washed with saturated brine solution (2 × 50 mL). The organic layer was then dried ($MgSO_4$), filtered and then concentrated *in-vacuo*. The resulting solution was then purified by column chromatography (SiO_2, 4:1 petroleum spirit: ethyl acetate) to give **257** as a yellow oil (7.3 g, 82 %) R_f = 0.76 (7:3 petrol/ethyl acetate). $[\alpha]_D^{35}$= 16.7 (*c* 1.7, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 2.07 (3H, s, C(=O)C**H**$_3$), 3.68-3.81 (3H, m, **H-2**, **H-3**, **H-5**), 3.86 (2H, dd, *J* = 9, 3, H6, H6'), 4.07 (1H, app.t, *J* = 9, 10, **H-4**), 4.51-4.57 (4H, m, PhC**H**$_2$O), 4.61-4.80 (3H, m, PhC**H**$_2$O), 4.89 (1H, d, *J* = 11, PhC**H**$_2$O), 6.23(1H, d, *J* = 2, **H-1**), 7.153-7.41(20H, m, Ar-**H**). ^{13}C-NMR (75.4 MHz, $CDCl_3$), δ = 21.5 (CH_3), 69.3

(PhCH$_2$O), 72.5 (PhCH$_2$O), 72.8 (PhCH$_2$O), 73.8 (PhCH$_2$O), 73.9 (C-2), 74.7 (C-3), 74.9 (C-4), 75.8 (C-6), 79.6 (C-5), 92.3 (C-1), 128.0(Ar C-H), 128.2(Ar C-H), 128.3(Ar C-H), 128.5 (2 × Ar C-H), 128.5 (Ar C-H), 128.8 (2 × Ar C-H), 129.4 (Ar C-H), 138.3 (Ar C), 138.6 (Ar C), 138.7 (Ar C), δ:169.4 (C=O). IR(liquid film) νmax (cm^{-1}) = 3055.2, 2867.2, 1957.5, 1875.1, 1750.2, 1604.1.HRMS (M+NH$_4$) calcd for $C_{36}H_{42}NO_7$ 600.2961, found 600.2961.

Preparation of 2,3,4,6-tetra-*O*-benzyl-1-thio-α-D-mannopyranoside 258[227]



Method 1

Benzyl mercaptan (0.99 mL, 9 mmol, 1.1 equiv) was added to acetate **257** (4.45 g, 7.62 mmol, 1 equiv) in dry DCM (20 mL). To this solution trimethylsilyl trifluoromethane sulfonate (1.68 mL, 9 mmol 1.1 equiv) was added. The reaction was stirred at 0 °C for 1 h and then allowed to reach room temperature. The reaction was quenched after 16 hours or when all staring material was consumed by the addition of triethylamine (1.21 mL, 9 mmol, 1.1 equiv), washed with saturated brine (2 × 25 mL) and water (2 × 25 mL). The organic layer was dried (MgSO$_4$), filtered and then concentrated *in-vacuo*. The crude product was then purified by column chromatography (SiO$_2$, ethyl acetate and petroleum spirit 60:40, using a gradient eluent system (9:1 – 7:3 petrol/ethyl acetate) to afford **258** (2.8 g, 56%), as a pale yellow oil Rf 0.84 (7:3 petrol/ethyl acetate).

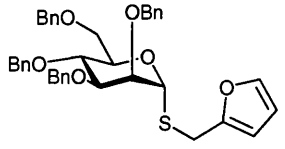
Method 2

Benzyl mercaptan (0.68 mL, 6 mmol 1.1 equiv) was added to acetate **257** (3.05 g, 5 mmol, 1 equiv) in dry DCM (20 mL). To this solution boron trifluoride

diethyletherate ($BF_3{\cdot}OEt_2$) (0.73 mL, 6 mmol, 1.1 equiv) was added. The reaction was initiated at 0 °C and then allowed to reach room temperature. The reaction was quenched after 16 hours or when all staring material was consumed. The reaction was quenched by washing with saturated sodium bicarbonate (2 × 50 mL), followed by water (2 × 25 mL) and saturated brine (2 × 25 mL). The organic layer was dried ($MgSO_4$), filtered and then concentrated *in vacuo*. The crude product was then purified by column chromatography (SiO_2, ethyl acetate and petroleum spirit 60:40), using a gradient eluent system (9:1 – 7:3 petrol/ethyl acetate) to afford **258** (2.4 g, 70%), as a while oily solid Rf 0.84 (7:3 petrol/ethyl acetate).

^{1}H-NMR (300 MHz, C_6D_6); δ = 3.4-3.6 (1H, app.d, *J* = 13.7, **H-2**), 3.6-3.76 (3H,m, **H-3**, **H-4**, **H-5**), 3.78-3.81 (dd, *J* = 10.5, 5.5, **H-6a**), 4.02-4.06 (1H dd, *J* = 9.4, 3.1, **H-6b**), 4.21-4.36 (5H, m, PhC**H**$_2$O, SC**H**$_2$), 4.37-4.56 (m, 5H, PhC**H**$_2$O), 4.9-5.0 (1H, d, *J* = 11.3, PhC**H**$_2$), (1H, as, **H-1**), 6.96-7.34 (25H, m, Ar-**H**). ^{13}C-NMR (75.4 MHz, C_6D_6), δ = 34.6 (SCH_2), 69.9 (**C-6**), 71.9 (**C-3**), 72.2 ($PhCH_2O$), 73.2 ($PhCH_2O$), 73.4 ($PhCH_2O$), 75.2 (**C-4**), 75.7 (**C-2**), 81.3 (**C-5, C-1**), 127.2 (Ar-**C**-H), 127.4 (Ar-**C**-H), 127.5 (Ar-**C**-H), 127.6 (Ar-**C**-H), 127.8 (Ar-**C**-H), 127.9 (Ar-**C**-H), 128.2 (Ar-**C**-H), 128.3 (2 × Ar-**C**-H), 128.4 (Ar-**C**-H), 128.6 (Ar-**C**-H), 129.4 (Ar-**C**-H), 138.2 (Ar-**C**), 138.6 (Ar-**C**), 138.8 (Ar-**C**), 139.1 (Ar-**C**), 139.4 (Ar-**C**). IR(liquid film) νmax (cm^{-1}) = 3062.6, 2865.0, 1951.3, 1880.1, 1810.7, 1723.3, 1602.5. HRMS (M+NH_4) calcd for $C_{41}H_{46}NSO_5$ 664.3097, found 664.3099. Anal. Calcd for $C_{41}H_{46}NSO_5$: C, 76.1 ; H, 6.5 Found C, 75.7 ; 6.8.

Preparation of 2,3,4,6-tetra-*O*-furfuryl-1-thio-α-D-mannopyranoside 260



Method 1

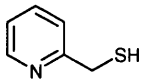
Furfuryl mercaptan (0.97 mL, 10 mmol 1.1 equiv) was added to acetate **257** (5.08g, 8.7 mmol, 1 equiv) in dry DCM (20 ml). To this solution trimethylsilyl trifluoromethane sulfonate (TMSOTf) (1.85 mL, 10 mmol 1.1 equiv) was added. The reaction was initiated at 0°C for and then allowed to reach room temperature. The reaction was quenched after 16 hours or when all staring material was consumed This was achieved by the addition of triethylamine (1.35 ml, 10 mmol, 1.1 equiv), the reaction mixture was then washed with saturated brine (2 × 25 mL) followed with water (2 × 25 mL). The organic layer was dried ($MgSO_4$), filtered and then concentrated *in-vacuo*. The crude product was then purified by column chromatography (SiO_2, ethyl acetate and petroleum spirit 60:40), using a gradient eluent system (9:1 – 7:3 petrol/ethyl acetate) to afford **260** (3.1g, 56%), as a deep orange oil R_f 0.86 (7:3 petrol/ethyl acetate).

Method 2

Furfuryl mercaptan (0.98 mL, 6.3 mmol, 1.1 equiv) was added to acetate **257** (3.05g, 5.7 mmol, 1 equiv) in dry DCM (20 ml). To this solution boron trifluoride diethyletherate (0.89 mL, 6.3 mmol, 1.1 equiv) was added. The reaction was stirred at 0 °C and then allowed to reach room temperature. The reaction was quenched after 16 hours or when all staring material was consumed by washing with saturated sodium bicarbonate (2 × 50 mL), followed by water (2 × 25 mL) and saturated brine (2 × 25 mL). The organic layer was dried ($MgSO_4$), filtered and then concentrated *in vacuo*. The crude product was then purified by column chromatography (SiO_2, ethyl acetate and petroleum spirit 60:40), using a gradient eluent system (9:1 – 7:3 petrol/ethyl acetate) to afford **260** (2.49g, 75%) as an orange oil in a 1:1 ratio of anomers, R_f 0.86 (7:3 petrol/ethyl acetate). $[\alpha]_D^{35}$= +87.5 (*c* 2, $CHCl_3$); ^{1}H-NMR ($CDCl_3$), 3.497 (1H, m, **H-5α**), 3.594 (1H, dd, *J* = 5.86, 4.30 **H-4α**), 3.73-3.94 (7H,

m, **H-5β**, **H-4β**, **H-2α**, **H-2β**, **H-3α**, **H-3β**, **H-6bβ**), 4.04 (3H, m, **H-6b**, **H-4β**, **H-5β**), 4.43 (1H, app.s, **H-1β**), 4.50-4.71 (13H, m, PhC**H**$_2$O), 4.88-4.94 (7H, m, PhC**H**$_2$O) , 5.41 (1H, app.s, **H-1α**), 6.23 (1H, app.d, *J*= 3.01 Hz FYR-**H2**), 6.30 (1H, app.dd, *J*= 1.884 Hz, 3.014 Hz, FYR-**H1**), 7.204-7.483 (21H m, Ar-**H**, FYR-**H3**) . ^{13}C-NMR ($CDCl_3$), δ = 27.2 (S**C**H$_2$), 70.2 (**C-6**), 72.6 (**C-3**), 73.9 (Ph**C**H$_2$O), 75.3 (Ph**C**H$_2$O), 75.6 (Ph**C**H$_2$O), 76.4 (**C-4**), 77.1 (Ph**C**H$_2$O), 80.7 (**C-5**), 82.6 (C-1β), 84.9 (**C-1α**), 100.7, 108.8 (FYR-**C2**), 110.9 (FYR-**C3**), 127.9 (Ar-**C**-H), 127.9 (Ar-**C**-H), 127.0 (Ar-**C**-H), 127.1 (Ar-**C**-H), 127.2 (Ar-**C**-H), 127.5 (Ar-**C**-H), 128.6 (Ar-**C**-H), 128.7 (Ar-**C**-H), 128.8 (Ar-**C**-H), 128.9 (Ar-**C**-H), 137.7 (Ar-**C**), 138.5 (Ar-**C**), 138.6 (Ar-**C**), 138.9 (Ar-**C**), 142.1, 142.8 (FYR-**C1**), 151.2 (FYR-**C4**). IR(liquid film) νmax (cm^{-1}) = 3083.8, 3036.8, 2919.2, 2860.5, 1952.7, 1876.4, 1810.7, 1734.4, 1701.1, 1603.6, 1585.9, 1496.3, 1453.7, 1397.5, 1364.7. HRMS (M+H) calcd for $C_{39}H_{40}O_6S$ 636.2546 found 636.3617. Anal. Calcd for $C_{39}H_{40}NO_6S$: C, 73.6 ; H, 6.3 Found C, 73.8 ; 6.5.

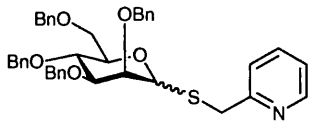
Preparation of 2-pyridinemethanethiol (262)[189]



Thiourea (5.10g, 67.1 mmol, 1.1 equiv) was added to a solution of 2-picolyl chloride hydrochloride (10g, 61 mmol, 1 equiv) in H_2O (50 mL). The reaction was stirred at 85-89 °C for 1h. The reaction mixture was then cooled to 5 °C and nitrogen was bubbled through the reaction mixture for 2 hrs maintaining the internal temperature below 10 °C. While maintaining the same flow of nitrogen, sodium hydroxide (7.32g, 183 mmoles, 3 eq) was added in 4 portions over two h whilst maintaining the inner temperature below 10 °C. The resulting mixture was stirred for 16 hrs under nitrogen at room temperature and then washed with *tert*-butylmethyl ether (2 ×

20mL). The aqueous phase was then decanted, cooled to 5 °C and the pH carefully adjusted to 7 with concentrated HCl. The aqueous layer was extracted with dichloromethane (2 × 50 mL) and the combined dichloromethane fractions where washed with saturated brine (50 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give **262** 7.68 *g* (70% yield), which was immediately used to prepare **6**. ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 1.95 (s 1H, SH), 3.74 (d 2H, J = 7.4, S-CH_2-pyr), 7.05 (1H m, H-β-pyr), 7.23 (1H m, H-δ-pyr), 7.50 (1H m, H-γ-pyr), 8.45 (1H m, H-α-pyr).^{13}C-NMR (75.4 MHz, $CDCl_3$), δ = 31.2 (HS**C**H_2Ph), 122.1(**C**-β-pyr), 122.5 (**C**-δ-pyr), 137.0 (Pyr-C-*ipso*), 149.5 (**C**-γ-pyr), 160.2 (**C**-α-pyr). IR(liquid film) νmax (cm^{-1}) (cm^{-1}) = 3280.6, 2856.0, 2556.0, 1673.8, 1513.1.

Preparation of 2,3,4,6-tetra-*O*-pyridinemethane-1-thio-α/β-D-mannopyranoside 259



Method 1

2-Pyridinemethane thiol (0.85g, 6.7 mmol, 1.1 equiv) was added to acetate **257** (3.56g, 6.1 mmol, 1 equiv) in dry DCM (20 ml). To this solution trimethylsilyl trifluoromethane sulphonate (1.29 mL, 6.7 mmol 1.1 equiv) was added. The reaction was stirred at 0 °C and then allowed to reach room temperature. The reaction was quenched after 16 hours or when all staring material was consumed. The reaction was quenched with triethylamine (0.94 ml, 6.7 mmol, 1.1 equiv), washed with saturated brine (2 × 25 mL) followed by two separate extractions with water (2 × 25 mL). The organic layer was dried ($MgSO_4$), filtered and then concentrated *in-vacuo*. The crude product was then purified by column chromatography (SiO_2, ethyl acetate and petroleum spirit 60:40), using a gradient eluent system (9:1 – 7:3 petrol/ethyl

acetate) to afford **259** (2.57g, 65%), as an orange oil with a 1:1.15 ratio of anomers (α:β), which were separated by the above chromatographic method Rf 0.37, 0.32 (7:3 petrol/ethyl acetate).

Method 2

2-Pyridylmethane thiol (0.72g, 5.7 mmol 1.1 equiv) was added to acetate **257** (3.02g, 5.2 mmol, 1 equiv) in dry DCM (20 ml) was added pyridyl mercaptan (0.72g, 5.7 mmol 1.1 equiv). To this solution boron trifluoride diethyletherate (0.72 mL, 5.7 mmol 1.1 equiv) was added. The reaction was initiated at 0 ^{O}C and then allowed to reach room temperature. The reaction was quenched after 16 hours or when all staring material was consumed. The reaction was quenched by washing with saturated sodium bicarbonate (2 × 50 mL), followed by two separate extractions with water (2 × 25 mL) and washed with saturated brine (2 × 25 mL). The organic layer was dried ($MgSO_4$), filtered and then concentrated *in-vacuo*. The crude product was then purified by column chromatography (SiO_2, ethyl acetate and petroleum spirit 60:40), using a gradient eluent system (9:1 – 7:3 petrol/ethyl acetate) to afford **259** as an orange oil comprising of a mixture of anomers (α:β 1:1.15)(3.18g, 98%), Rf 0.37, 0.32 (α, β) (7:3 petrol/ethyl acetate).

Analysis for 2,3,4,6-tetra-*O*-pyridinemethane-1-thio-α-D-mannopyranoside

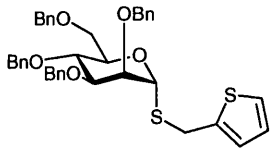
$[\alpha]_D^{35}$= +58.3 (*c* 0.4, $CHCl_3$); ^{1}H NMR (300MHz $CDCl_3$): δ = 3.50 (1H, dd, *J* = 2, 10.9 Hz, **H-3**), 3.69-3.72 (5H, m, **H-2**, **H-5**, **H-6a, H-6b**), 3.86-4.06 (3H m, S**CH$_2$**), 4.41-4.49 (4H, m, PhOC**H$_2$**), 4.60-4.51 (3H, m, PhOC**H$_2$**), (1H, d, *J* = 11, PhOC**H$_2$**), 5.35 (1H, d, *J* = 2, **H-1),** 7.04-7.295 (22H, m, Ar-**H**), 7.49 (1H, app.td, *J*= 2, 2, 8, **H-γ-pyr**), 7.47 (1H, app.d, *J*= 5, **H-α-pyr**), 8.47 (1H, app.d, *J*= 5, **H-α-pyr**). ^{13}C (75 MHz $CDCl_3$): δ = 37.1 (S**C**H$_2$PYR), 69.5 (**C-6**), 72.3 (C-3), 72.4 (Ph**C**H$_2$), 72.8

(PhCH$_2$), 73.7 (PhCH$_2$), 75.3 (**C-4**), 75.5 (PhCH$_2$), 76.3 (**C-2**), 80.7 (**C-5**), 81.8 (**C-1**), 122.4 (pyr-**β**C), 123.7 (pyr-**δ**C), 127.9 (Ar **C**-H), 128.0 (2 × Ar **C**-H), 128.2 (Ar **C**-H), 128.3 (2 × Ar **C**-H), 128.8 (Ar **C**-H), 129.7 (Ar **C**-H), 137.0 (pyr-**γ**C), 138.3 (Ar **C**), 138.5 (Ar-**C**), 138.8 (Ar-**C**), 138.9 (Ar-**C**), 150.1 (**C**-γ-pyr), 158.2 (**C**-α-pyr). IR(liquid film) vmax (cm^{-1}) = 3001.6, 2866.8, 1953, 1876.1, 1811.1, 1724.5, 1590.4. HRMS (M+H) calcd for $C_{40}H_{42}NSO_5$ 648.2783, found 648.2782. Anal. Calcd for $C_{40}H_{42}NSO_5$: C, 74.2 ; H, 6.4 ; N, 2.2Found C, 73.5 ; 6.2 ; N, 2.1

Analysis for 2,3,4,6-tetra-*O*-pyridinemethane-1-thio-β-D-mannopyranoside

$[\alpha]_D^{35}$= -64.8 (*c* 1.7, $CHCl_3$); ^{1}H NMR (300 MHZ $CDCl_3$): δ = 3.39-3.45 (1H, m, **H-5**), 3.53 (1H, dd, *J* = 3, 9, **H-3**), 3.70-3.78 (2H, m, **H-2**, **H-6**), 3.88-3.94 (3H, m, **H-4**, **H-6**), 4.11-4.15 (1H, m, SC**H$_2$**), 4.42(1H, app.s, SC**H$_2$**), 4.54-4.58 (2H, m, PhC**H$_2$**O), 4.60 (1H, d, *J* = 1, **H-1**), 4.62-4.67 (2H, m, PhC**H$_2$**O), 4.81-4.96 (3H, m, PhC**H$_2$**O), 7.11-7.38 (22H, m, Ar-H,), 7.44-7.47 (2H, m,), 7.53-7.59 (1H, td, *J* = 2, 8). ^{13}C NMR (75 MHZ $CDCl_3$): 37.1 (SCH$_2$PYR), 70.2 (**C-6**), 72.6 (**C-3**), 73.8 (PhCH$_2$O), 75.3 (PhCH$_2$O), 75.6 (PhCH$_2$O), 76.6 (**C-4**), 77.9 (**C-2**), 80.4 (**C-5**), 82.8 (**C-1α**), 84.7 (**C-1β**), 122.3 (pyr-**β**C), 124.1 (pyr-**δ**C), 127.9 (Ar-**C**-H), 128.1 (Ar-**C**-H), 128.2 (Ar-**C**-H), 128.5 (Ar-**C**-H), 128.6 (Ar-**C**-H), 128.7 (Ar-**C**-H), 128.8 (2 × Ar-**C**-H), 137.0 (Ar-**C**), 138.4 (Ar-**C**), 138.6 (Ar-**C**), 138.7 (Ar-**C**), 138.8 (Ar-**C**), 150.1 (**C**-γ-pyr), 158.5 (**C**-α-pyr). IR(cm^{-1}) Liquid Film: vmax (cm^{-1}) 3048.5, 2860.5, 1954.3, 1877.9, 1807.4, 1736.9. HRMS (M+H) calcd for $C_{40}H_{42}NSO_5$ 648.2784, found 648.2786. Anal. Calcd for $C_{40}H_{42}NSO_5$: C, 74.2 ; H, 6.4 ; N, 2.2 Found C, 73.7 ; 6.3 ; N, 2.0

Preparation of 2,3,4,6-tetra-*O*-thienyl- 1-thio-α-D--thiomethylthiophenyl thiomannopyranoside 261.



Method 1

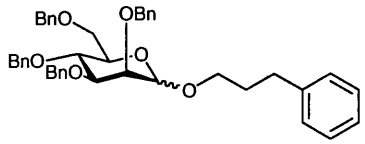
2-Thenyl mercaptan (0.78 g, 9.6 mmol, 1.1 equiv) was added to acetate **257** (5.08 g, 8.7 mmol, 1 equiv) in dry DCM (20 ml). To this solution trimethylsilyl trifluoromethane sulphonate (1.85 mL, 9.6 mmol, 1.1 equiv) was added. The reaction was initiated at 0 ^{O}C and then allowed to reach room temperature. The reaction was quenched after 16 hours or when all staring material was consumed. The reaction was quenched with triethylamine (1.35 mL, 9.6 mmol, 1.1 equiv), washed with saturated brine (2 × 25 mL) water (2 × 25 mL). The organic layer was dried ($MgSO_4$), filtered and then concentrated *in-vacuo*. The crude product was then purified by column chromatography (SiO_2, ethyl acetate and petroleum spirit 60:40), using a gradient eluent system (9:1 – 7:3 petrol/ethyl acetate) to afford **261** (2.8 g, 49%), as a brown oil with R_f 0.90 (7:3 petrol/ethyl acetate).

Method 2

2-Thenyl mercaptan (0.46 mL, 5.7 mmol, 1.1 equiv) was added to acetate **257** (3.05 g, 5.2 mmol, 1 equiv) in dry DCM (20 ml). To this solution boron trifluoride diethyletherate (1.68 mL, 5.7 mmol, 1.1 equiv) was added. The reaction was stirred at 0 $^{\circ}$C and then allowed to reach room temperature. The reaction was quenched after 16 hours or when all staring material was consumed. The reaction was quenched by washing with saturated sodium bicarbonate (2 × 50 mL), followed with water (2 × 25 mL) and washed with saturated brine (2 × 25 mL). The organic layer was dried ($MgSO_4$), filtered and then concentrated *in-vacuo*. The crude product was then

purified by column chromatography (SiO_2, ethyl acetate and petroleum spirit 60:40), using a gradient eluent system (9:1 – 7:3 petrol/ethyl acetate) to afford **261** (3.81g, 67%), Rf 0.90 (7:3 petrol/ethyl acetate). $[\alpha]_D^{35}$= +61.3 (*c* 0.8, $CHCl_3$). ^1H NMR (300 MHZ $CDCl_3$): δ =3.72 (1H, dd, *J* = 2, 11 **H-3**), 3.76-4.16 (7H, m, **H-2**, **H-4**, **H-5**, **H-6a**, **H-6b**, SCH_2), 4.51-4.57 (5H, m, $PhCH_2O$), 4.61-4.72 (2H, m, $PhCH_2O$), 4.91 (1H, d, *J* = 11, $PhCH_2O$), 5.38 (app.s, **H-1**), 6.88-6.97 (3H, m, 3 × thiophene C-**H**), 7.18-7.46 (20H, m, Ar-**H**). ^{13}C-NMR ($CDCl_3$), δ = 29.5 (SCH_2), 69.5 (**C-6**), 72.1 ($PhCH_2O$), 72.4 ($PhCH_2O$), 72.9 (**C-3**), 73.8 ($PHCH_2O$), 75.3 (**C-4**), 75.6 ($PhCH_2O$), 76.1 (**C-2**), 80.8 (**C-5**), 81.2 (**C-1**), 126.9 (Ar-**C**-H), 127.1 (Ar-**C**-H), 127.2 (2 × Ar-**C**-H), 127.9 (Ar-**C**-H), 128.1 (Ar-**C**-H), 128.2 (Ar-**C**-H), 128.4 (2 × Ar-**C**-H), 128.7 (Ar-**C**-H), 128.8 (2 × Ar-**C**-H), 128.9 (Ar-**C**-H), 129.4 (Ar-**C**-H). 138.2 (Ar-**C**), 138.7 (Ar-**C**), 138.8 (Ar-**C**). IR(liquid film) νmax (cm^{-1}) =3062.3, 2864.7, 1951.2, 1875.2, 1810.2, 1750.6, 1604.0.

Preparation of 2,3,4,6-tetra-*O*-benzyl-1-*O*-phenylpropyl-α-D-mannopyranoside (264)



Method 1 –I_2 Activation protocol

259 (100 mg, 0.15 mmol, 1 equiv) was dissolved in dry DCM (5 mL), and to this I_2 (44 mg, 0.17 mmol, 1.1 equiv) was added along with 3-phenyl propan-1-ol (23 mg, 0.16 mmol, 1.1 equiv), potassium carbonate (24 mg, 0.17 mmol, 1.1 equiv) and 200 mg of 3Å activated molecular sieves. The reaction was stirred at room temperature until completion of the reaction. The solids present where removed by filtration, and the filtrate was washed with saturated sodium thiosulphate (1 × 25 mL). The

resulting solution was concentrated *in-vacuo* and then purified via column chromatography (SiO_2, 3:1 hexane/ethyl acetate) to afford **264** as the α-anomer of (69 mg, 67%), as a pale orange oil $R_f = 0.81$ (7:3 petrol/ethyl acetate).

Method 2 –$Cu(OTf)_2$ Activation

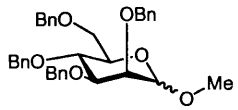
To copper(II) triflate (35 mg, 0.1 mmol, 1.1 equiv) was added thioglycoside (**259**) (57 mg, 0.09 mmol, 1 equiv) and 3-phenyl propan-1-ol (23 mg 0.17 mmol, 2.2 equiv) in dry DCM (10 mL). The reaction was maintained at reflux through out. Initially an emerald green coloured solution resulted, which gradually turned brown as the reaction proceeded. The reaction was monitored for 3 hrs by TLC. The reaction mixture was then diluted with DCM (10 mL) quenched by washing with saturated sodium bicarbonate (1 X 25 mL), dried ($MgSO_4$), filtered and then concentrated *in-vacuo*. Purification via column chromatography on silica (gradient method, petrol; petrol: ethyl acetate 7:3) afforded **264** (49 mg, 85%), as a plale orange oil R_f 0.81.

Method 3- Attempted TfOH activation

To Triflic acid (7.3 μL, 5.9 mmol, 1.1 equiv) was added thioglycoside (**264**) (57 mg, 0.09 mmol, 1 equiv) and 3-phenyl propan-1-ol (23 mg 0.17 mmol, 2.2 equiv) in dry DCM (10 mL). The reaction was maintained at reflux through out. Initially a dark brown collared. The reaction was monitored for 3 hrs by TLC. The reaction mixture was then diluted with DCM (10 mL) quenched by washing with saturated sodium bicarbonate (1 × 25 mL), dried ($MgSO_4$), filtered and then concentrated *in-vacuo*. The crude reaction mixture was then analyzed by ^1H and ^{13}C NMR spectroscopy the result of which was that there was no anomeric signal present which corresponded to the known data achieved for the *O*-glycoside product. ^1H-NMR ($CDCl_3$), δ = 1.72-1.81 (2H, m, $OCH_2CH_2C\mathbf{H_2}Ph$), 2.46-2.68 (2H, m, $OCH_2C\mathbf{H_2}CH_2Ph$), 3.25-3.32 (1H, m, $\mathbf{OCH^1}H^2$), 3.57- 3.72 (5H, m **H2, H3, H4, H5, OCH^{1}H^2**), 3.81-3.85 (1H,

dd, J = 3.01, 9.49, **H-6a**), 3.79-3.94 (1H, m, **H-6b**), 4.43 (1H, d, J = 7.54), 4.61 (1H, d, J = 8.67, PhC**H**$_2$O), 4.66 (2H app.d , J = 3.39, PhC**H**$_2$O), 4.77 (1H, d, J = 1.88, **H-1**), 4.81 (1H, d J = 10.926, PhC**H**$_2$O), 7.04-7.32 (25H, m, Ar-**H**). ^{13}C-NMR ($CDCl_3$), δ = 31.4 (PhCH$_2$**C**H$_2$CH$_2$O), 32.8 (Ph**C**H$_2$CH$_2$CH$_2$O), 67.2 (PhCH$_2$O), 69.7 (PhCH$_2$CH$_2$CH$_2$O), 72.3 (**C-2**), 72.6 (PhCH$_2$O), 72.9 (PhCH$_2$O), 73.7 (PhCH$_2$O), 75.2 (**C-3**), 75.4 (**C-4**), 76.9 (**C-6**), 77.0 (**C-5**), 98.3 (**C-1**), 126.2 (Ar-**C**-H), 127.9 (Ar-**C**-H), 128.0 (Ar-**C**-H), 128.1 (Ar-**C**-H), 128.2 (3 × Ar-**C**-H), 128.4 (Ar-**C**-H), 128.6 (Ar-**C**-H), 128.7 (2 × Ar-**C**-H), 128.82(Ar-**C**-H), 138.8 (Ar-**C**), 138.9 (Ar-**C**). IR(liquid film) νmax (cm^{-1}) = 3027.7, 2915.3, 1958.3, 1875.4, 1811.8, 1735.5. HRMS (M+NH$_4$) calcd for $C_{36}H_{42}NO_7$ 676.3638, found 676.3632. Anal. Calcd for $C_{36}H_{42}O_7$: C, 78.4 ; H, 7.04 Found C, 77.5 ; H, 6.73.

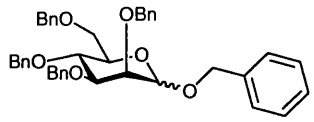
Preparation of 2,3,4,6-tetra-*O*-benzyl-1-*O*-methyl-α-D-mannopyranoside 193



To copper(II) triflate (35 mg, 0.1 mmol, 1.1 equiv) was added thioglycoside (**259**) (57 mg, 0.09 mmol, 1 equiv) and methanol (6 mg 0.2 mmol, 2.2 equiv) in dry DCM (10 mL). The reaction was maintained at reflux throughout. Initially an emerald green coloured solution resulted, which gradually turned brown as the reaction proceeded. The reaction was monitored for 3 h by TLC. The reaction mixture was then diluted with DCM (10 mL) quenched by washing with saturated sodium bicarbonate (1 × 25 mL), dried ($MgSO_4$), filtered and then concentrated *in-vacuo*. Purification via using column chromatography on silica (gradient method petrol; petrol: ethyl acetate 7:3) afforded (**264**) (47 mg, 96%) as a pale orange oil. ^{1}H NMR spectroscopy showed that within the recognized detection limits only the α-anomer was observed.

$[\alpha]_D^{35}$= +22.8 (*c* 1, $CHCl_3$); ^1H NMR (300MHz, $CDCl_3$): σ = 3.35 (3H, s, OMe), 3.45-3.57 (1H, m, **H-5**), 3.52-3.75 (3H, m, **H-2**, **H-3**, **H-4**) (, 3.81 (1H, dd, *J* = 3, 9 **H-6b**), 3.90 (2H, m, **H-6a**) 4.36-4.66 (6H, m, Ph**C**H_2O), 4.81 (2H, d, *J* = 11, Ph**C**H_2O), 5.12 (1H, d, *J* = 2, **H-1**), 7.07-7.32 (20H, m, Ar-**H**). ^{13}C NMR (75 MHz): 55.1 (O**M**e), 72.1 (**C-6**) (73.8 (**C-2**), 73.9 (Ph**C**H_2O), 74.9 (Ph**C**H_2O), 75.3 (Ph**C**H_2O), 75.4 (**C-3**), 75.5 (**C-4**), 80.6 (**C-5**), 99.3 (**C-1**), 127.9 (Ar-**C**-H), 127.9 (Ar-**C**-H), 128.0 (Ar-**C**-H), 128.0 (Ar-**C**-H), 128.1 (Ar-**C**-H), 128.2 (Ar-**C**-H), 128.2 (Ar-**C**-H), 128.3 (Ar-**C**-H), 128.4 (Ar-**C**-H), 128.5 (Ar-**C**-H), 128.7 (Ar-**C**-H), 128.8 (Ar-**C**-H), 138.0 (Ar-**C**), 138.7 (Ar-**C**), 138.8 (Ar-**C**), 138.9 (Ar-**C**), 138.9 (Ar-**C**). IR(liquid film) νmax (cm^{-1}) : 3087.2, 3029.2, 2910.9, 2888.8, 1951.6, 1875.1, 1811.1, 1734.4, 1605.2, 1585.6, 1496.2, 1453.3, 1362.6, 1308.2, 1207.8, 1098.7 HRMS (M+NH_4) calcd for $C_{35}H_{42}NO_6$ 572.3012, found 572.3012. Anal. Calcd for $C_{35}H_{42}O_6$: C, 75.8 ; H, 6.91 Found C, 75.5 ; H, 6.79.

Preparation of 1,2,3,4,6-penta-1-*O*-Benzyl-α-D-mannopyranoside[194]

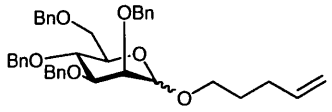


To copper(II) triflate (35 mg, 0.1 mmol, 1.1 equiv) was added thioglycoside (**259**) (57 mg, 0.09 mmol, 1 equiv) and benzyl alcohol (21 mg 0.2 mmol, 2.2 equiv) in dry DCM (10 mL). The reaction was maintained at reflux throughout. Initially an emerald green coloured solution resulted, which gradually turned brown as the reaction proceeded. The reaction was monitored for 3 h by TLC. The reaction mixture was then diluted with DCM (10 mL) quenched by washing with saturated sodium bicarbonate (1 × 25 mL), dried ($MgSO_4$), filtered and then concentrated in vacuo. Purification via using column chromatography on silica (gradient method petrol; petrol: ethyl acetate 7:3) afforded **264** (47 mg, 97%) as a pale yellow oil. ^1H

NMR spectroscopy showed that within the recognized detection limits only the α-anomer was observed.

$[\alpha]_D^{35}$= +36 (*c* 1.2, $CHCl_3$)^{1}H NMR (300MHz): δ = 3.63-3.71 (2H, m, **H-3**, **H-4**), 3.73-3.78 (2H, m, **H-2**, **H-5**), 3.87 (1H, dd, *J* = 3, 9, **H-6a**), 3.94 (1H, app.t, *J* = 9, **H-6b**), 4.40 (1H, d, *J* = 6, BnOC**H**$_2$), 4.45 (1H, d, *J* = 3, BnOC**H**$_2$), 4.53 (2H, app.s, BnOC**H**$_2$), 4.59 (1H, app.s, BnOC**H**$_2$), 4.61-4.65 (3H, m, BnOC**H**$_2$), 4.80 (1H, d, *J* = 11, BnOC**H**$_2$), 4.9 (1H, d, *J* = 2, **H-1**), 7.03-7.06 (25H, m, Ar-**H**), ^{13}C NMR (75.4MHz, $CDCl_3$): δ = 69.3 (BnO**C**H$_2$), 69.6, (**C-6**), 72.5, (**C-3**), 72.8 (PhO**C**H$_2$), 73.0 (PhO**C**H$_2$), 73.8 (PhO**C**H$_2$), 75.0 (**C-4**), 75.4 (PhO**C**H$_2$), 75.6 (**C-2**), 80.6 (**C-5**) , 97.6 (**C-1**), 127.9 (Ar-**C**-H), 127.9 (Ar-**C**-H), 128.0 (Ar-**C**-H), 128.1 (Ar-**C**-H), 128.2 (2 × Ar-**C**-H), 128.3 (Ar-**C**-H), 128.5 (Ar-**C**-H), 128.7 (3 × Ar-**C**-H), 128.8 (Ar-**C**-H), 128.9 (Ar-**C**-H), 137.7 (Ar-**C**), 138.8(2 × Ar-**C**), 138.9 (2 × Ar-**C**), 139.1 (Ar-**C**). IR (Liquid film) vmax (cm^{-1}) = 3087.2, 2888.8, 1951.6, 1875.1, 1811.1, 1734.4, 1605.2, 1585.6. HRMS (M+NH_4) calcd for $C_{41}H_{46}NO_6$ 648.3325, found 648.3324. Anal. Calcd for $C_{36}H_{42}O_7$: C, 78.1 ; H, 6.71 Found C, 77.5 ; H, 6.77.

Preparation of 2,3,4,6-tetra-*O*-benzyl-1-*O*-pentenyl-α-D-mannopyranoside[228]

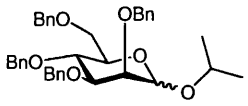


To copper(II) triflate (35 mg, 0.1 mmol, 1.1 equiv) was added thioglycoside (**259**)(57 mg, 0.09 mmol, 1 equiv) and 5-pentene-1-ol (17 mg 0.2 mmol, 2.2 equiv) in dry DCM (10 mL). The reaction was maintained at reflux through out. Initially an emerald green coloured solution resulted, which gradually turned brown as the reaction proceeded. The reaction was monitored for 3 hrs by TLC. The reaction mixture was then diluted with DCM (10 mL) quenched by washing with saturated sodium bicarbonate (1 × 25 mL), dried ($MgSO_4$), filtered and then concentrated in

vacuo. Purification via using column chromatography on silica (gradient method petrol; petrol: ethyl acetate 7:3) afforded **264** (49 mg, 98%) as a pale orange oil. ^{1}H NMR spectroscopy showed that within the recognized detection limits only the α-anomer was observed.

$[\alpha]_D^{35}$= +4.8 (*c* 3.3, $CHCl_3$) ^{1}H NMR (300MHz, $CDCl_3$) : δ = 1.18 – 1.37 (1H, m, $OCH_2CH_2CH_2CH{=}CH_2$), 1.49 – 1.72 (3H, m, $OCH_2CH_2CH_2CH{=}CH_2$), 1.94 – 2.12 (2H, m, $OCH_2CH_2C\mathbf{H_2}CH{=}CH_2$), 3.63 – 3.81 (5H, m, **H-2**, **H-3**, **H-4**, **H-5,** $OC\mathbf{H_2}CH_2$), 3.83 (1H, dd, *J* = , **H-6b**), 3.88 – 3.96 (1H, m, **H-6a**), 4.49 - 4.23 (2H, m, $BnOC\mathbf{H_2}$), 4.52 - 4.63 (3H, m, $BnOC\mathbf{H_2}$), 4.66 (1H, d, *J* = 2, **H-1**), 4.78 (1H, app.t $CH{=}C\mathbf{H_2}$, *J* = 2, 3), 4.81 - 4.90 (2H, m, $PhC\mathbf{H_2}O$), 4.91 - 4.99 (1H, m, $CH{=}C\mathbf{H_2}$), 5.62 - 5.83 (1H, m, $OCH_2CH_2CH_2C\mathbf{H}{=}CH_2$), 7.07 - 7.41 (20H, m, Ar-**H**). ^{13}C NMR (75MHZ): δ = 29.0 ($OCH_2CH_2\mathbf{C}H_2CH{=}CH_2$), 30.7 ($OCH_2\mathbf{C}H_2CH_2CH{=}CH_2$), 67.3 ($O\mathbf{C}H_2CH_2CH_2CH{=}CH_2$), 69.7 (**C-6**), 72.2 (**C-3**), ($Ph\mathbf{C}H_2O$), 72.6, ($Ph\mathbf{C}H_2O$), 73.0 ($Ph\mathbf{C}H_2O$), 73.7($Ph\mathbf{C}H_2O$), 75.2 (**C-4**), 75.4 (**C-2**), 75.6, (**C-5**), 98.3, (**C**-1), 115.2 ($CH{=}\mathbf{C}H_2$), 127.9, (Ar-**C**-H), 128.0, (Ar-**C**-H), 128.1, (Ar-**C**-H), 128.2, (2 × Ar-**C**-H), 128.3, (Ar-**C**-H), 128.4, (Ar-**C**-H), 128.5, (Ar-**C**-H), 128.7, (3 × Ar-**C**-H), 128.8, (Ar-**C**-H), 138.4, (Ar-**C**), 138.8, (Ar-**C**), 139.0, (Ar-**C**). IR (Liquid film) νmax (cm^{-1}) = 3046.5, 2879.2, 1949.9, 1875.0, 1810.9, 1726.5, 1640.0 1585.6. HRMS ($M+NH_4$) calcd for $C_{39}H_{48}NO_6$ 626.3482, found 626.3481. Anal. Calcd for $C_{39}H_{44}O_6$: C, 76.9 ; H, 7.26 Found C, 76.4 ; H, 7.67.

Preparation of 2,3,4,6-tetra-O-benzyl-1-*O*-isopropyl-α-D-mannopyranoside[229]

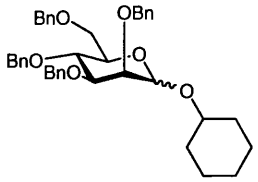


To copper(II) triflate (35 mg, 0.1 mmol, 1.1 equiv) was added thioglycoside (**259**)(57 mg, 0.09 mmol, 1 equiv) and propan-2-ol (12 mg, 0.2 mmol, 2.2 equiv) in dry DCM

(10 mL). The reaction was maintained at reflux through out. Initially an emerald green coloured solution resulted, which gradually turned brown as the reaction proceeded. The reaction was monitored for 3 h by TLC. The reaction mixture was then diluted with DCM (10 mL) quenched by washing with saturated sodium bicarbonate (1 × 25 mL), dried ($MgSO_4$), filtered and then concentrated *in-vacuo.* Purification via using column chromatography on silica (gradient method petrol; petrol: ethyl acetate 7:3) afforded (**264**) (49 mg, 97%) as a pale yellow oil. ^{1}H NMR spectroscopy showed that within the recognized detection limits only the α-anomer was observed.

$[\alpha]_D^{35}$= +36.1 (*c* 1.3, $CHCl_3$); ^{1}H NMR (300 MHZ): 0.98 (3H, d, *J* = 6, $OCH(CH_3)_2$), 1.1 (3H, d, *J* = 6, $OCH(CH_3)_2$), 3.62 – 3.67 (2H, m, **H-2**, **H-3**), 3.71 (1H, app.t, *J* = 5, 7, **H-4**), 3.76 (1H, dd, *J* = 1, 5, **H-5**), 3.84 (1H, dd, *J* = 3, 12, **H-6b**), 3.89 – 3.95 (1H, app.t, *J* = 9, **H-6a**), 4.40 – 4.48 (2H, m, $PhCH_2O$), 4.56-4.58 (3H, m, $PhCH_2O$), 4.62 (1H, m, $PhCH_2O$), 4.78 – 4.82 (2H, d, *J* = 11, $PhCH_2O$), 4.86, (1H, d, *J* = 2, **H-1**), 7.06 – 7.32, (20H, m Ar-**H**). ^{13}C (75 MHz): δ = 21.6 (CH_3), 23.6 (CH_3), 69.3, $OCH(CH_3)_2$, 69.7 (**C-6**), 72.1 (**C-3**), 72.5 ($PhCH_2O$), 73.0, ($PhCH_2O$), 73.7, ($PhCH_2O$), 75.5 ($PhCH_2O$,**C-4**), 75.6, (**C-2**), 80.8 (**C-5**), 96.2 (**C-1**), 127.8, (Ar-**C**-H), 127.9, (Ar-**C**-H), 128.0, (Ar-**C**-H), 128.2, (Ar-**C**-H), 128.3, (Ar-**C**-H), 128.5, (Ar-**C**-H), 128.7, (2 × Ar-**C**-H), 138.9, (Ar-**C**), 138.1 (Ar-**C**). IR(Liquid film) νmax (cm^{-1}): 3086.5, 2917.9, 1949.8, 1875.4, 1811.1, 1734.2, 1640.5, 1607.2. HRMS (M+NH_4) calcd for $C_{37}H_{46}NO_6$ 600.3325, found 600.3318. Anal. Calcd for $C_{37}H_{42}O_6$: C, 76.3 ; H, 7.26 Found C, 76.0 ; H, 7.49.

Preparation of 2,3,4,6-tetra-O-benzyl-1-*O*-cyclohexyl-α-D-mannopyranoside[230]



Method 1- I_2 activation

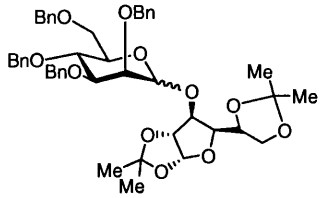
100 mg of (**259**) was dissolved in 5 mL of dry DCM, to this 1.1 equivalents of I_2 (40 mg) was added along with 1.1 equivalents of both cyclohexanol (0.015 ml, 0.1 mmol) and potassium carbonate (K_2CO_3) (18 mg, 0.1 mmol). To this 200 mg of activated molecular sieves where added (3Å). The reaction was stirred at room temperature until completion of the reaction. The solids where removed by filtration, and the filtrate was washed with sodium thiosulphate (Na_2SO_4) (2 × 25 mL) and water (1 × 25 mL) the resulting solution was dried ($MgSO_4$) concentrated *in-vacuo* then purified by column chromatography (SiO_2, using ethyl acetate: hexane as the solvent system of choice (1:3). Giving the cyclohexane mannopyranoside (67 mg, 70%), as an orange oil R_f = 0.7 (7:3 petrol : ethyl acetate).

Method 2- $Cu(OTf)_2$

To copper(II) triflate (35 mg, 0.1 mmol, 1.1 equiv) was added thioglycoside (**259**) (57 mg, 0.09 mmol, 1 equiv) and cyclohexanol (17 mg 0.2 mmol, 2.2 equiv) in dry DCM (10 mL). The reaction was maintained at reflux through out. Initially an emerald green coloured solution resulted, which gradually turned brown as the reaction proceeded. The reaction was monitored for 3 hrs by TLC. The reaction mixture was then diluted with DCM (10 mL) quenched by washing with saturated sodium bicarbonate (1 × 25 mL), dried ($MgSO_4$), filtered and then concentrated in vacuo. Purification via using column chromatography on silica (gradient method petrol; petrol: ethyl acetate 7:3) afforded in 92% (55 mg, 92%) as a pale orange oil.

^{1}H NMR spectroscopy showed that within the recognized detection limits only the α-anomer was observed. $[\alpha]_D^{35}$= +30.7 (*c* 1.5, $CHCl_3$); ^{1}H NMR (300MHz, $CDCl_3$): δ = 1.04 – 1.77 (10H, m), 3.35 – 3.51 (1H, m OC**H**$(CH_2)_2$, 3.63 – 3.79 (4H, m **H-2, H-3, H-4, H-5**), , 3.89 (2H, m, **H-6a**, **H-6b),** 4.41 – 4.48 (2H, m, PhC**H**$_2$O), 4.57 (2H, m, PhC**H**$_2$O), 4.61 (1H, m, PhC**H**$_2$O), 4.64 – 4.72 (2H, m , PhC**H**$_2$O), 4.80 (1H, d, *J* = 11, PhC**H**$_2$O), 4.92 (1H, d, *J* = 2, **H-1**), 7.07 – 7.32 (20H, m, Ar-H). ^{13}C NMR (75MHZ, $CDCl_3$): δ = 24.2, (**C**H_2), 24.4, (**C**H_2), 26.0, (**C**H_2), 31.7 (**C**H_2), 33.7, (OCH(**C**$H_2)_2$), 69.8 (**C-6**), 72.1, (**C-2**), 72.6, (Ph**C**H_2O), 73.0, (Ph**C**H_2O), 73.7, (Ph**C**H_2O), 75.1, (**C-3**), 75.6, (Ph**C**H_2O), 75.7, (**C-4**), 77.9 (O**C**H$(CH_2)_2$, 80.7 (**C-5**), 96.1, (**C-1**), 127.8, (Ar-**C**-H), 127.9, (2 × Ar-**C**-H), 128.00, (Ar-**C**-H), 128.1, (2 × Ar-**C**-H), 128.3, (Ar-**C**-H), 128.5, (Ar-**C**-H), 128.7, (3 × Ar-**C**-H), 138.9, (Ar-**C**), 139.0 (Ar-**C**). IR (Liquid film) νmax (cm^{-1}): 3029.5, 2931.7, 2857.0, 1950.7, 1874.8, 1808.0, 1726.4, 1605.0, 1585.7. HRMS (M+NH_4) calcd for $C_{40}H_{50}NO_6$ 640.3638, found 640.3642. Anal. Calcd for $C_{36}H_{42}O_7$: C, 77.1 ; H, 7.44 Found C, 76.5 ; H, 7.42.

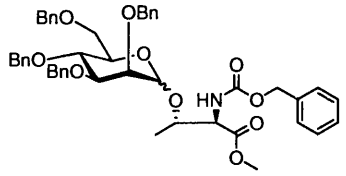
Preparation of 2,3,4,6-tetra-*O*-benzyl-1-*O*-diacetone-α-D-glucose-α-D-mannopyranoside



To copper(II) triflate (34 mg, 0.1 mmol, 1.1 equiv) was added thioglycoside (**259**)(57 mg, 0.08 mmol, 1 equiv) and diacetone-D-glucose (50 mg 0.19 mmol, 2.2 equiv) in dry DCM (10 mL). The reaction was maintained at reflux through out. Initially an emerald green coloured solution resulted, which gradually turned brown as the reaction proceeded. The reaction was monitored for 3 h by TLC. The reaction

mixture was then diluted with DCM (10 mL) quenched by washing with saturated sodium bicarbonate (1 × 25 mL), dried ($MgSO_4$), filtered and then concentrated in vacuo. Purification via using column chromatography on silica (gradient method petrol; petrol: ethyl acetate 7:3) afforded 2,3,4,6-tetra-O-benzyl-1-*O*-(diacetone-α-D-glucose)-(1-3)-α-D-mannopyranoside in 16% (11 mg, %) as a pale yellow oil. ^1H NMR (300MHz, $CDCl_3$): δ = 1.14 (3H, s, **Me**), 1.18 (3H, s, **Me**), 1.25 (3H, s, **Me**), 1.33 (3H, s, **Me**), 3.61-3.77 (7H, m,), 3.88-4.02 (3H, m,), 4.36-4.97(10H, m, $PhCH_2O$, **H-1**), 4.82 (1H, d, *J* = 11, $PhCH_2O$), 7.07-7.32 (20H, m, **Ar-H**).

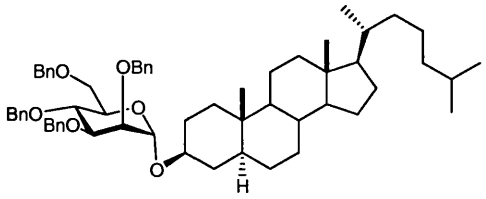
Preparation of 2,3,4,6-tetra-*O*-benzyl-1-*O*-α-D-mannopyranoside



To copper(II) triflate (35 mg, 0.1 mmol, 1.1 equiv) was added thioglycoside (**259**) (57 mg, 0.08 mmol, 1 equiv) and (23 mg 0.19 mmol, 2.2 equiv) in dry dichloromethane (10 mL). The reaction was maintained at reflux through out. Initially an emerald green collared solution resulted, which gradually turned brown as the reaction proceeded. The reaction was monitored for 3 h by TLC. The reaction mixture was then diluted with dichloromethane (10 mL) quenched by washing with saturated sodium bicarbonate (1 × 25 mL), dried ($MgSO_4$), filtered and then concentrated *in-vacuo*. Purification via using column chromatography on silica (gradient method petrol; petrol: ethyl acetate 7:3) afforded 2,3,4,6-tetra-*O*-benzyl-1-*O*-α-D-mannopyranoside in 85% (49 mg, 85%) as white needle like crystals. ^1H NMR spectroscopy showed that within the recognized detection limits only the α-anomer was observed: m.p. 91-93 °C; $[\alpha]_D^{35}$= +33 (*c* 0.3, $CHCl_3$); ^1H NMR

(300MHz, $CDCl_3$): δ = 1.20 (3H, m, *J* = , OCH(C**H**$_3$)CHN), 3.46 (1H, app.t, *J* = 3, 2, **H-2**), 3.49 (3H, s, $CO_2C\mathbf{H}_3$), 3.56 – 3.73 (4H, m, **H-3**, **H-4**, **H-5**, **H-6b**), 3.87 (1H, app.t, *J* = 9, **H-6a**), 4.20 – 4.27 (2H, m, OC**H**(CH$_3$)CHN, PhOC**H**$_2$), 4.46 (1H, app.s, PhOC**H**$_2$), 4.41 (1H, bs, PhOC**H**$_2$), 4.57 (2H, m, PhOC**H**$_2$), 4.75 – 4.80 (2H, m, PhOC**H**$_2$, **H-1**), 5.18 (1H, d, *J* = 9, OCH(CH$_3$)C**H**N), 7.06 – 7.33 (25H, m). ^{13}C NMR (75MHZ): δ = 18.9 (Me), 52.7 (C-H), 59.0 (C-H), 67.7(**C-6**), 69.5 (**C-3**), 72.8 (PhC**H**$_2$O), 73.77(PhC**H**$_2$O), 74.8 (PhC**H**$_2$O), 75.2 (**C-4**), 76.7 (**C-2**), 79.7 (**C-5**), 99.9 (**C-1**), 127.9 (Ar-**C**-H), 128.1 (Ar-**C**-H), 128.3 (Ar-**C**-H), 128.5 (Ar-**C**-H), 128.6 (Ar-**C**-H), 128.7 (Ar-**C**-H), 128.8 (Ar-**C**-H), 129.0 (Ar-**C**-H), 136.5 (Ar-**C**), 138.5 (Ar-**C**), 138.6 (Ar-**C**), 138.7 (Ar-**C**), 156.9 (NH**C**=O), 171.4 (O**C**=O). IR(Liquid Film) vmax (cm^{-1}): 3448.1, 3048.5, 2931.0, 2860.5, 1954.3, 1883.8, 1719.2, 1590.0, 1490.1, 1443.1, 1372.5, 1266.8. HRMS (M+NH$_4$) calcd for $C_{47}H_{51}NO_{10}$ 789.3515, found 789.3518.

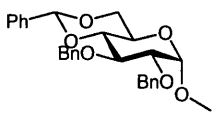
Preparation of 2,3,4,6-tetra-*O*-benzyl-1-*O*-dihydrocholestanol-α-D-mannopyranoside[229]



To copper(II) triflate (35 mg, 0.1 mmol, 1.1 equiv) was added thioglycoside (**259**) (57 mg, 0.09 mmol, 1 equiv) and β-cholestanol (23 mg 1.9 mmol, 2.2 equiv) in dry dichloromethane (10 mL). The reaction was maintained at reflux through out. Initially an emerald green coloured solution resulted, which gradually turned brown as the reaction proceeded. The reaction was monitored for 3 h by TLC. The reaction mixture was then diluted with dichloromethane (10 mL) quenched by washing with saturated sodium bicarbonate (1 × 25 mL), dried ($MgSO_4$), filtered and then

concentrated in vacuo. Purification via using column chromatography on silica (gradient method petrol; petrol: ethyl acetate 7:3) afforded 2,3,4,6-tetra-*O*-benzyl-1-*O*-dihydrocholestanol-α-D-mannopyranoside in 85% (49mgs, 85%) as a white solid (m.p. 91-93 °C). ^{1}H NMR spectroscopy showed that within the recognized detection limits only the α-anomer was observed. $[\alpha]_D^{35}$= +25.2 (*c* 1.7, $CHCl_3$); ^{1}H NMR (300 MHz): δ = 0.48-1.97 (46H, m, β-cholestanol), 3.42-3.55 (1H, m, O-CH β-cholestanol), 3.63-3.93 (6H, m, **H-2**, **H-3**, **H-4**, **H-5**, **H-6a**, **H-6b**), 4.40-4.48 (2H, m, PhC**H**$_2$O), 4.55-4.61 (3H, m, PhC**H**$_2$O), 4.65-4.71 (2H, m, PhC**H**$_2$O), 4.80 (1H, d, *J* = 11, PhC**H**$_2$O), 4.94 (1H, d, *J* = 2, **H-1**), 7.07-7.32 (20H, m, Ar-**H**). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.5 (Me), 12.7 (2 × Me), 19.1 (Me), 21.6 (Me), 22.3 (CH_2), 23.3 (CH_2), 24.3 (CH_2), 24.6 (CH_2), 28.4 (CH_2), 28.7 (CH_2), 29.1 (CH_2), 35.9 (CH_2), 36.0 (CH_2), 36.2 (CH_2), 36.6 (CH_2), 39.9 (CH_2), 40.5 (CH_2), 43.0 (CH_2), 45.3 (CH_2), 54.7 (CH_2), 56.7, 56.9, 69.8 (**C-6**), 72.5 (**C-3**), 73.0 ($PhCH_2O$), 73.7 ($PhCH_2O$), 75.6 (**C-4**), 77.7 (**C-2**), 80.8 (**C-5**), 96.2 (**C-1**), 127.8 (Ar-**C**-H), 127.9 (Ar-**C**-H), 128.0 (Ar-**C**-H), 128.1 (Ar-**C**-H), 128.2 (Ar-**C**-H), 128.5 (Ar-**C**-H), 128.7 (Ar-**C**-H), 128.7 (Ar-**C**-H), 138.9 (Ar-**C**), 138.9 (Ar-**C**), 139.1 (Ar-**C**). IR(Liquid Film) νmax (cm^{-1}): 3060.8, 2919.8, 1730.9, 1602.5, 1496.5, 1496.5, 1463.6, 1376.9. HRMS ($M+NH_4$) calcd for $C_{61}H_{86}NO_6$ 928.6455, found 928.6450. Anal. Calcd for $C_{61}H_{82}O_6$: C, 80.4 ; H, 9.07 Found C, 79.5 ; H, 9.18.

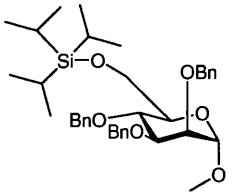
Preparation of 2,3-dibenzyl-4,6-benzylidene-1-*O*-methoxy-α-D-glucopyranoside



To 4,6-benzylidene-α-D-methoxyglucopyranose 253 (3.06 g, 11 mmol, 1 equiv) in dry DMF (20 mL) was added NaH [40% w/w dispersion in mineral oil] (1.302 g, 33

mmol, 3 equiv). To this solution was added benzyl bromide (3.8 mL, 33 mmol, 3 equiv). The reaction was monitored by TLC until the starting material was consumed. The reaction mixture was diluted with ethyl acetate (40 mL) then washed with water (3 × 100ml), dried ($MgSO_4$), filtered then concentrated to give a viscous orange oil. The product was crystallized by the addition of a minimum amount of ethyl acetate and then subsequent addition of n-pentane. This gave **254** as a white crystalline solid (4.8 g, 96% yield). ^1H NMR (300MHz, $CDCl_3$): δ = 3.43 (3H, s, OMe), 3.58 (1H, dd, *J* = 4, 11, **H-2**), 3.76 (1H, app.t *J* = 9, 11, **H-4**), 3.73 (1H, app.t, *J* = 10, **H-6a**), 3.79-3.90 (1H, m , **H-5**), 4.08 (1H, app.t *J* = 9, **H-3**), 4.29 (1H, d, *J* = 4, **H-1**), 4.72 (1H, d, *J* = 12, PhC**H**$_2$O), 4.82-4.90 (2H, m, PhC**H**$_2$O), 4.94 (1H, d, PhC**H**$_2$O), 5.78 (1H, s, PhC**H**O$_2$), 7.27-7.58 (15H, m, Ar-**H**). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.7 (C-2), 62.7 (C-5), 69.5 (C-6), 74.2 (Ph**C**H$_2$O), 75.8 (PhCH$_2$O), 79.0 (**C-3**), 79.5 (**C-4**), 99.6 (**C-1**), 101.7 (Ph**C**HO$_2$), 126.4 (Ar-**C**-H), 128.0 (Ar-**C**-H), 128.3 (Ar-**C**-H), 128.5 (Ar-**C**-H), 128.6 (Ar-**C**-H), 128.7 (Ar-**C**-H), 128.7 (Ar-**C**-H), 128.9 (Ar-**C**-H), 129.1 (Ar-**C**-H), 129.3 (Ar-**C**-H), 129.4 (Ar-**C**-H), 137.8 (Ar-**C**), 138.5 (Ar-**C**), 139.1 (Ar-**C**). IR(Liquid film) νmax (cm^{-1}) = 3189.5, 2919.2, 2837.0, 1731.0, 1648.7, 1460,7, 1378.4. Anal. Calcd for $C_{36}H_{42}O_7$: C, 72.7 ; H, 6.54 Found C, 72.5 ; H, 6.51.

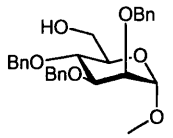
Preparation of 2,3,4-tri-*O*-benzyl-6-*O*-triisopropylsilyl-1-*O*-methyl-α-D-mannopyranoside



To α-D-methoxymannose (7.58 g, 39.1 mmol, 1 equiv) in dry DMF (50 mL) was added triisopropylsilyl chloride (9.2 mL , 43 mmol, 1.1eq). To this solution was

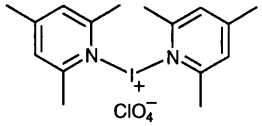
added imadazole (5.9 g, 86 mmol, 2.2eq) the reaction mixture was stirred overnight at room temperature. The reaction mixture was then diluted with Dichloromethane (100mL) and extracted with water (3 × 100ml). The extracts where then dried ($MgSO_4$) and concentrated in vacuo to give a viscous, pale yellow oil. The oil was dissolved in of dry DMF (50mL) and to this was added of benzyl bromide (21 mL, 235 mmol, 6eq) followed by the portionwise addition of sodium hydride [40% dispersion in mineral oil] (9.4 g, 235 mmol, 6equiv) over a 2h period at room temperature. After the final addition of hydride the reaction was stirred under nitrogen for 4 hours again at room temperature. The reaction mixture was diluted with ice cold water (100 mL) and extracted with dichloromethane (3 × 100mL). The mixture was then concentrated in vacuo and purified by column chromatography (gradient method (peterol-petherol:ethyl acetate 7:3) to yield **264** (14.5 g, 63%) as a yellow viscous oil. $[\alpha]_D^{35}$= +11.2 (*c* 1.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.18 (18H, d, *J* = 3, **Me**), 1.74 (3H, s, MeC**H**), 3.39 (3H, s, O**Me**), 3.69 (1H, m, **H-4**), 3.86 (1H, m, **H-5**), 4.01 (4H, m, **H-2**, **H-3**, **H-6'**, **H-6''**), 4.63 (3H, app.s, PhC**H**$_2$O), 4.69-4.73 (3H, m, PhC**H**$_2$O), 4.74 (1H, d, *J* = 2, **H-1**), 4.82 (3H, m, PhC**H**$_2$O), 5.02 (1H, d, *J* = 11, PhC**H**$_2$O), 7.34-7.46 (15H, m, Ar-**H**). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 12.48 ^{i}Pr(**Me**), 18.5 **C**H(Me)$_2$, 54.9 (O**Me**), 63.7 (C-6) 72.6 (**C-3,** PhCH$_2$O), 72.9 (PhCH$_2$O), 73.8 (**C-4**), 75.2 (PhCH$_2$O), 75.4 (**C-2**), 80.8 (**C-5**), 99.1 (**C-1**), 127.9 (Ar-**C**-H), 128.0 (Ar-**C**-H), 128.1 (Ar-**C**-H), 128.2 (Ar-**C**-H), 128.5 (Ar-**C**-H), 128.7 (Ar-**C**-H), 128.8 (Ar-**C**-H), 128.9 (Ar-**C**-H), 128.9 (Ar-**C**-H), 129.0 (Ar-**C**-H), 138.8 (Ar-**C**), 139.0 (Ar-**C**), 139.2 (Ar-**C**). IR(liquid film) vmax (cm^{-1}) = 3036.8, 2863.8, 1949.3, 1874.7, 1807.9, 1722.6, 1604.9. HRMS (M+NH_4) calcd for $C_{36}H_{42}NO_7$ 638.3877, found 638.3881. Anal. Calcd for $C_{36}H_{42}O_7$: C, 71.5 ; H, 8.44 Found C, 72.6 ; H, 7.77.

Preparation of 2,3,4-tri-*O*-benzyl-1-*O*-methyl-α-D-mannopyranoside[231]



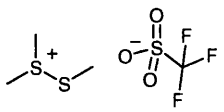
To a solution of **254** (1.53 g, 3 mmol, 1 equiv) in DCM (10 mL) was added TBAF [1M, in THF] (10 mL, 10 mmol, 3.32 equiv). The reaction mixture was initiated at 0°C and then warmed to 50°C after 30 mins. The reaction mixture was monitored by TLC for 5 h until the disappearance of the starting material was observed. The reaction mixture was then diluted with DCM (100 mL) then washed with of water (3 × 50ml). The extract was then concentrated *in-vacuo* and purified by column chromatography on silica (gradient elution petrol: ethyl acetate 1:0-7:3), to give **269** (1.05 g, 82%) as a pale yellow viscous oil. $[\alpha]_D^{35}$= +16.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.19 (1H, bs, C-6-O**H**), 3.33 (3H, s, O**CH$_3$**), 3.62 – 3.38 (1H, m, **H-3**), 3.78 – 3.84 (2H, m, H**6-a**,H**6-b**), 3.88 (1H, dd, *J* = 3, 12, **H-2**), 3.93 (1H, dd, *J* = 3, 9, **H-4**), 4.01 (1H, app.t, *J* = 9, **H-5**), 4.66 (2H, app.s, PhO**CH$_2$**), 4.72 (2H, d, *J* = 8, PhO**CH$_2$**), 4.74 (1H, d, *J* = 2, **H-1**), 4.81 (1H, d, *J* = 12, Ph**CH$_2$**O), 4.98 (1H, d, *J* = 11, Ph**CH$_2$**O), 7.27 – 7.41 (15H, m Ar-H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 55.2 (O**CH$_3$**), 62.8 (**C-6**), 72.4 (**C-3**), 72.6 (Ph**C**H$_2$O), 73.4 (Ph**C**H$_2$O), 75.1 (Ph**C**H$_2$O), 75.3 (**C-4**), 75.6 (Ph**C**H$_2$O), 77.1 (**C-2**), 80.6 (**C-5**), 99.71 (**C-1**), 128.0 (Ar-**C**-H), 128.1 (Ar-**C**-H), 128.2 (Ar-**C**-H), 128.4 (Ar-**C**-H), 128.8 (Ar-**C**-H), 128.8 (Ar-**C**-H), 138.64 (Ar-**C**), 138.8 (Ar-**C**), 138.9 (Ar-**C**). IR (Liquid film) νmax (cm^{-1}): 3471.6, 3048.5,3025, 2907.5, 1954.3, 1877.9, 1813.2, 1719.2, 1604.7, 1584.1. Anal. Calcd for $C_{36}H_{42}O_7$: C, 75.4 ; H, 6.74 Found C, 73.9 ; H, 7.00.

Preparation of Iodonium Di-sym-Collidine Perchlorate (IDCP)[43]



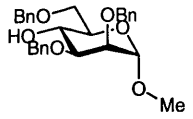
To a solution of *sym*-collidine (20 ml, 150 mmol, 1 equiv) in water (100 mL) was added with stirring silver nitrate (9.13 g, 54 mmol, 0.36 equiv) sodium perchlorate (11.21 g, 92 mmol, 0.61 equiv) this instantaneously gave a white precipitate which was the washed with water (200 mL) then ethanol (100 mL) and finally diethyl ether (100ml). The product was then dried over phosphorus pentoxide under high vacuum to give silver di-*sym*-collidine perchlorate (24.05 g 100%). This was then taken up in chloroform (200 mL) and treated with iodine (12.98 g, 51 mmol, 0.34 equiv). A second amount of *sym*-collidine (5 ml, 38 mmol) was added. After 15 mins the yellow precipitate of silver iodide was removed by filtration and the iodonium complex was crystallized from the filtrate by cooling. The product was filtered and to the filtrate was added a small amount of ether which gave further white crystals. The combined crystals were then dried under high vacuum.

Preparation of dimethyl (methylthio) trifluoromethanesulphonate (DMTST)[202]



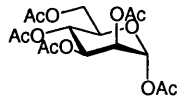
To a solution of dimethyl sulphide (3.22 ml, 44 mmol, 1 equiv)) in DCM (20 mL) was added methyl triflate (2.25 mL, 44 mmol, 1 eq). The reaction mixture was stirred at room temperature for 48 h. The product was precipitated from solution by the addition of diethyl ether to give white crystals of dimethyl(methylthio)sulphoniuim trifluoromethanesulphonate, m.p.56-57°C (7.1 g, 95%). The product was stored under nitrogen and kept at –15°C. δ(100 MHz, CD_2Cl_2) 3.27 (6H, s) and 2.93(3H, s)

2,3,6-tri-*O*-benzyl-1-*O*-methyl-α-D-mannopyranoside[195]



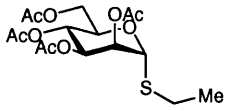
Trifluoroacetic acid (2.75mL, 37 mmol, 6 equiv) was added dropwise to a solution of **254** (3.30g, 7.14 mmol,) and triethylsilane (5.7ml, 31 mmol, 6 equiv) in dichloromethane (20mL) at 0 °C. When the addition was complete the reaction was warmed to room temperature until the starting material was consumed (4 hr). The solution was diluted with ethyl acetate (30 mL) then washed with aqueous saturated sodium bicarbonate (50 mL) and brine (50 ml) then dried ($MgSO_4$) filtered and concentrated in vacuo. The product was purified by column chromatography on silica 100:0 – 70:30 petrol: ethyl acetate 7:3) to afford **265** as a pale yellow viscous oil (2.65 g, 80 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.96 (1H, bs, C-4-OH), 3.29 (3H, s, O**Me**), 3.31-3.38 (2H, m, **H-6',H-6''**), 3.43 (1H, dd, *J* = 3, 9, **H-2**), 3.55 (1H, app.t, *J* = 9, **H-4**), 3.73-3.79 (1H, m, **H-5**), 4.42 (1H, dd, *J* = 6, 12 **H-3**), 4.47 (1H, d, *J* = 2, **H-1**), (2H, app.d, *J* = 3, PhC**H**$_2$O), 4.57 (1H, d, *J* = 9, PhC**H**$_2$O), 4.60 (3H, s, PhC**H**$_2$O), 4.63 (2H, app.t, *J* = 12, 14), 4.95 (1H, d, *J* = 11, PhC**H**$_2$O), 7.18-7.31 (20H, m, Ar-H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 55.7 (O**Me**), 68.9 (**C-6**), 70.1 (**C-3**), 73.2 (Bn**C**H$_2$O),73.6 (Ph**C**H$_2$O) 75.9 (Ph**C**H$_2$O),77.6 (**C-2**) 80.1 (**C-5**), 81.1 (**C-4**), 98.4 (**C-1**), 128.2 (Ar-**C**), 128.3 (Ar-**C**), 128.4 (Ar-**C**), 128.5 (Ar-**C**), 128.6 (Ar-**C**), 128.9 (Ar-**C**-H), 138.8 (Ar-**C**), 138.1 (Ar-**C**), 138.2 (Ar-**C**). IR (Liquid film) vmax (cm^{-1}): 3501.6, 3045.2, 2917.5, 1944.6, 1873.1, 1818.4, 1725.5, 1611.3, 1587.2.

Preparation of 1,2,3,4,6-penta-*O*-acetyl-α-D-mannopyranoside[232]



Pyridine (64 mL, 787 mmol, 14 equiv) was added to a solution of D-mannose (10.12 g, 56 mmol) in DMF (100 mL). To this solution was added acetic anhydride (35 mL, 334 mmol 7 equiv) at 0 °C. The reaction was stirred for 6 h. The crude product was then left on a steam bath overnight, then crystallised from ethyl acetate/ petroleum ether to give pentaacetate:m.p. 82-84 °C; (20.83 g, 95%).$[\alpha]_D^{35}$= +27.1 (*c* 0.84, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 1.90 (3H, s, AcMe), 1.95 (3H, s, AcMe), 1.98 (3H, s, AcMe), 2.08 (6H, s, AsMe), 3.93-4.02 (2H, m, **H-5** , **H-6a),** 4.18 (1H, dd, *J* = 5.5, **H-6b**), 5.15-5.19 (1H, m, **H-2**), 5.23-5.31 (2H, m, **H-3**, **H-4**), 5.97 (1H, d, *J* = 2, **H-1**). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 20.9 (AcMe), 21.1 (AcMe), 21.2 (2 × AcMe), 62.4 (**C-6**), 65.8 (**C-2**), 68.6 (**C-3**), 69.0 (**C-4**), 70.9 (**C-5**), 90.9 (**C-1**), 168.4 (**C**=O), 169.9 (**C**=O), 170.0 (**C**=O), 170.3 (**C**=O), 170.9 (**C**=O). IR(Liquid film) vmax (cm^{-1}): 2963.8, 2921.4, 2853.5, 1739.3, 1455.0, 1370.1.

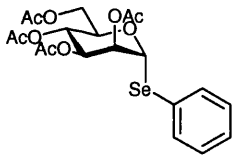
Preparation of 2,3,4,6-tetra-*O*-acetyl-ethyl-1-thio-α-D-mannopyrannosidec 286[232, 233]



To pentaacetate (2.26 g, 5.8 mmol) in dry DCM (20 mL) was added ethane thiol (0.65 ml, 8.7 mmol, 1.5 eq,) and the mixture cooled to 0 °C in an ice bath. To this cooled solution was added of borontrifluoride diethyl etherate (0.81 mL, 6.4 mmol, 1.1 equiv). The reaction was allowed to warm to room temperature and was monitored by TLC until completion. The reaction mixture was quenched by washing with saturated sodium hydrogen carbonate (2 × 50mL). The

reaction mixture was then diluted with DCM (30 mL) then extracted with water (50 mL) then of saturated brine (50 mL). The organic layer was then dried ($MgSO_4$), filtered and concentrated *in-vacuo*. Purification via column chromatography on silica (100:0 – 7:3 petrol : ethyl acetate) afforded **286** (1.71 g, 75 %) as a pale yellow solid: m.p. 93-95 °C; $[\alpha]_D^{35}$= +36.7 (*c* 2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.45 (3H, t, *J* = 8, SCH_2CH_3) 1.92 (1H, s, Me), 1.99 (1H, s, Me), 2.03 (1H, s, Me), 2.10 (1H, s, Me), 2.71-2.48 (2H, m, SCH_2CH_3), 4.03 (1H, dd, *J* = 2, 12, **H-6b**), 4.25 (1H, dd, *J* = 5, 12, **H-6a**), 4.33 (1H, m, **H-5**), 5.23 (4H, m, **H-1**, **H-2**, **H-3**, **H-4**). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 15.2 (**Me**), 21.0(Ac**Me**), 21.1 (Ac**Me**), 21.1 (Ac**Me**), 21.4 (Ac**Me**), 25.9 ($MeCH_2$), 62.8 (**C-6**), 66.8, 69.3 (**C-3 & C-4**), 69.9 (**C-2**), 71.6 (**C-5**), 82.7 (**C-1**), 170.2 (O**C**(O)Me), 170.2 (O**C**(O)Me), 170.4 (O**C**(O)Me). IR(Liquid film) νmax (cm^{-1}) = 2929.9, 2862.0, 2301.8, 1743.5, 1459.2, 1425.2, 1378.6. Anal. Calcd for $C_{36}H_{42}O_7$: C, 49.0 ; H, 6.16 Found C, 48.9 ; H, 6.24.

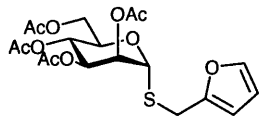
Preparation of 2,3,4,6-tetra-*O*-acetyl-1-phenyl-seleno-α-D-mannopyranoside 287[232, 233]



To pentaacetate (2.26g, 5.8 mmol) in dry DCM (20 mL) was added phenyl selenol (0.85 ml, 8.7 mmol, 1.5 eq,) and the mixture cooled to 0 °C in an ice bath. To this cooled solution was added borontrifluoride diethyl etherate (1.04 mL, 0.81 mmol, 1.1 equiv). The reaction was allowed to warm to room temperature and was monitored by TLC until completion. The reaction mixture was quenched by washing with saturated sodium hydrogen carbonate (2 × 50 mL). The reaction mixture was then diluted with DCM (30 mL) then extracted with water

(50ml) then of saturated Brine (50 ml). The organic layer was then dried ($MgSO_4$), filtered and concentrated *in-vacuo*. Purification via column chromatography on silica (100:0 – 7:3 petrol : ethyl acetate) afforded **287** (2.31 g, 82%) as a pale yellow solid; m.p. 75-77 °C; $[\alpha]_D^{35}$= +35.5 (*c* 2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.95 (3H, s, Me), 1.99 (3H, s, Me), 2.01 (3H, s, Me), 2.07 (3H, s, Me), 4.02 (1H, dd, *J* = 2, 12, **H-6a**), 4.25 (1H, dd, *J* = 6, 12, **H-6b**), 4.42-4.37 (1H, m, **H-5**), 5.26 (1H, dd, *J* = 3, 9, **H-3**), 5.28 (1H, at, *J* = 9, 10, **H-4**), 5.50 (1H, dd, *J* = 2, 3), 5.69 (1H, d, *J* = 2, **H-1**), 7.18-7.28 (3H, m, Ar-H), 7.48-7.58 (2H, m, Ar-H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 21.3 (Ac**Me**), 21.1 (Ac**Me**), 21.0 (Ac**Me**), 62.7 (Bn**C**H_2Se), 66.6 (**C-6**), 70.1 (**C-3**), 71.5 (**C-4**), 71.8 (**C-2**), 82.9 (**C-1**), 128.7 (Ar-**C**-H), 129.6 (Ar-**C**-H), 129.7 (Ar-**C**-H), 134.7 (Ar-**C**), 170.1 (O**C**(O)Me), 170.3 (O**C**(O)Me), 170.3 (O**C**(O)Me), 171.0 (O**C**(O)Me). IR(Liquid film) νmax (cm^{-1}) = 3048.7, 2929.9, 2878.9, 2123.6, 1951.5, 1752.0, 1573.8, 1455.0, 1382.8. Anal. Calcd for $C_{36}H_{42}O_7$: C, 49.29 ; H, 4.96 Found C, 49.0 ; H, 4.96.

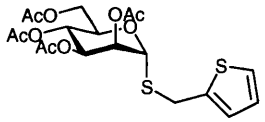
Preparation of 2,3,4,6-tetra-*O*-acetyl-1-furfuryl-thio-α-D-mannopyranoside 288



To pentaacetate (2.26 g, 5.8 mmol) in dry DCM (20 mL) was added furfuryl mercaptan (0.88 mL, 8.7 mmol, 1.5 eq,) and the mixture cooled to 0 °C in an ice bath. To this cooled solution was (0.81 ml 1.1 eq) of borontrifluoride diethyl etherate (0.81 mL, 6.4 mmol, 1.1 equiv). The reaction was allowed to warm to room temperature and was monitored by TLC until completion. The reaction mixture was quenched by washing with saturated sodium hydrogen carbonate (2 × 50mL). The reaction mixture was then diluted with DCM (30 mL)

then extracted with water (50mL) then of saturated Brine (50 mL). The organic layer was then dried ($MgSO_4$), filtered and concentrated *in-vacuo*. Purification via column chromatography on silica (100:0 – 7:3 petrol : ethyl acetate) afforded **288** (1.34 g, 52%) as an orange oil. $[\alpha]_D^{35}$= +29.2 (*c* 2, $CHCl_3$)^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.02 (3H, s, Ac**Me**), 2.06 (3H, s, Ac**Me**), 2.10 (3H, s, Ac**Me**), 2.18 (3H, s, Ac**Me**), 4.01-4.07 (3H, m, **H-5, H-2, H-3**), 4.11 (1H, dd, *J* = 2, 12, **H-6a**), 4.29 (2H, dd, *J* = 5, 12, **H-6b**), 5.27 (2H, app.t, *J* = 3,2, Fyr **H-3, H-4**), 5.34-5.36 (2H, m, FYR **H-1, H-2**), 6.09 (1H, d, *J* = 1, **H-1**). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 21.0 (Ac**Me**), 21.1 (Ac**Me**), 21.2 (Ac**Me**), 21.3 (Ac**Me**), 62.5 SCH_2-FYR), 65.9 (**C-6**), 68.7 (**C-3**), 69.1 (**C-4**), 71.0 (**C-2**), 91.0 (**C-1**), 168.5 (**C**=O), 170.0 (**C**=O), 170.4 (**C**=O), 171.1 (**C**=O). IR(Liquid film) νmax (cm^{-1}) = 3048.5, 2978.0, 1760.4, 1423.7, 1370.5, 1255.9 Anal. Calcd for $C_{36}H_{42}O_7$: C, 50.2 ; H, 5.15 Found C, 49.5 ; H, 5.48.

Preparation of 2,3,4,6-tetra-*O*-acetyl-α-D-1-thiophenyl-thio-mannopyrannoside 289



To of pentaacetate (2.26 g, 5.8 mmol) in dry DCM (20 mL) was added 2-thenyl mercaptan (0.71 ml, 8.7 mmol, 1.5 eq,) and the mixture cooled to 0 °C in an ice bath. To this cooled solution was added borontrifluoride diethyl etherate (0.81 mL, 6.4 mmol, 1.1 equiv). The reaction was allowed to warm to room temperature and was monitored by TLC until completion. The reaction mixture was quenched by washing with saturated sodium hydrogen carbonate (2 × 50 mL). The reaction mixture was then diluted with DCM (30 mL) then extracted with water (50 mL) then of saturated Brine (50mL). The organic layer was then dried ($MgSO_4$), filtered and concentrated *in-vacuo*. Purification via column chromatography on silica

(100:0 – 7:3 petrol : ethyl acetate) afforded **289** (1.68g, 63%) as an orange oil. $[\alpha]_D^{35}$= +26.1 (*c* 2, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.98 (3H, s, Ac**Me**), 2.05 (3H, s, Ac**Me**), 2.11 (3H, s, Ac**Me**), 2.14 (3H, s, Ac**Me**), 3.92-4.09 (3H, m, **H-6a**, **H-6b**, **H-5**), 4.30-4.36 (2H, m, **H-3**, **H-4**), 4.41 (1H, dd, *J* = **H-2**), 5.19 (1H, d, *J* = 2, **H-1**), 5.23-5.29 (2H, m, PhC**H**$_2$O), 5.34 (1H, dd, *J* = 3, 12 Thiophene **H-3**), 6.92 (1H, dd, *J* = 1, 2, thiophene **H-2**), 7.22-7.24 (1H, dd, *J* = 1, 5, Thiophene **H-1**). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 21.0 (Ac**Me**), 21.1 (**Ac**Me), 21.2 (Ac**Me**), 21.3 (Ac**Me**), 29.4, 62.7 (S**C**H$_2$C), 66.6 (**C-6**), 69.6 (**C-3**), 70.0 (**C-2**), 71.1 (**C-4**), 81.8 (**C-1**), 126.0 (Thiophene **C**), 127.3 (Thiophene **C**), 127.5 (Thiophene **C**), 140.0 (thiophene **C-*ipso***), 170.1 (**C**=O), 170.2 (**C**=O), 170.3 (**C**=O), 171.0 (**C**=O). IR(Liquid film) vmax (cm^{-1}) = 2887.4, 2853.5, 1739.3, 1459.2, 1374.3. Anal. Calcd for $C_{36}H_{42}O_7$: C, 48.4 ; H, 4.97 Found C, 49.1 ; H, 5.26.

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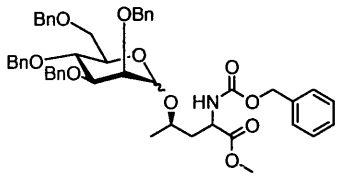
Appendices

5 Appendices

Table 1. Crystal data and structure refinement for 1.



Identification code	k02mcw3
Empirical formula	C47 H51 N O10
Formula weight	789.89
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P1
Unit cell dimensions	a = 10.2200(1)Å α = 106.273(1)°
	b = 14.2020(2)Å β = 99.098(1)°
	c = 15.3340(2)Å γ = 103.262(1)°
Volume	2019.73(4) $Å^3$
Z	2
Density (calculated)	1.299 Mg/m^3
Absorption coefficient	0.091 mm^{-1}
F(000)	840
Crystal size	0.40 x 0.25 x 0.08 mm
Theta range for data collection	3.61 to 27.49°
Index ranges	-12<=h<=13; -18<=k<=18; -19<=l<=19
Reflections collected	40702
Independent reflections	16869 [R(int) = 0.0719]
Reflections observed (>2σ)	13273
Data Completeness	0.994
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00 and 0.80
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	16869 / 3 / 1050
Goodness-of-fit on F^2	0.984
Final R indices [I>2σ(I)]	R_1 = 0.0453 wR_2 = 0.1005
R indices (all data)	R_1 = 0.0676 wR_2 = 0.1120
Absolute structure parameter	0.2(5)
Largest diff. peak and hole	0.243 and -0.210 $eÅ^{-3}$

Hydrogen bonds with H..A < r(A) + 2.000 Angstroms and <DHA > 110 deg.

D-H	d(D-H)	d(H..A)	<DHA	d(D..A)	A
N1-H1	0.880	2.233	160.90	3.078	O9A [x+1, y+1, z]
N1A-H1A	0.880	2.142	167.92	3.008	O9 [x, y-1, z]

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for 1.U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	X	y	z	U(eq)
O(1)	6437(1)	8893(1)	9218(1)	24(1)
O(2)	7380(1)	11129(1)	10035(1)	25(1)
O(3)	5488(2)	11436(1)	8806(1)	27(1)
O(4)	4830(2)	9516(1)	7220(1)	26(1)
O(5)	5992(2)	7061(1)	7716(1)	31(1)
O(6)	2700(2)	6710(1)	11365(1)	43(1)
O(7)	5010(2)	7238(1)	11745(1)	38(1)
O(8)	5014(2)	10677(1)	12933(1)	30(1)
O(9)	2851(2)	9794(1)	12045(1)	29(1)
O(10)	4639(1)	8997(1)	9981(1)	23(1)
O(16)	223(2)	1427(1)	8526(1)	27(1)
O(1A)	1519(1)	-954(1)	9052(1)	24(1)
O(2A)	2355(1)	1298(1)	9766(1)	28(1)
O(4A)	-515(2)	-556(1)	7089(1)	28(1)
O(5A)	1107(2)	-2789(1)	7621(1)	30(1)
O(6A)	-2596(2)	-3211(1)	11021(1)	44(1)
O(7A)	-183(2)	-2759(1)	11638(1)	35(1)
O(8A)	35(2)	592(1)	13031(1)	28(1)
O(9A)	-2134(2)	-290(1)	12138(1)	28(1)
O(10A)	-189(1)	-848(1)	9909(1)	23(1)
N(1)	4702(2)	9182(1)	11862(1)	24(1)
N(1A)	-241(2)	-754(1)	11786(1)	24(1)
C(1)	5980(2)	9486(2)	9942(1)	22(1)
C(2)	5979(2)	10525(2)	9848(1)	21(1)
C(3)	5232(2)	10424(2)	8868(1)	22(1)
C(4)	5712(2)	9729(2)	8122(1)	23(1)
C(5)	5639(2)	8710(2)	8293(1)	23(1)
C(6)	4545(2)	8095(2)	10264(1)	23(1)
C(7)	3665(3)	7163(2)	9437(2)	33(1)
C(8)	3909(2)	8261(2)	11101(1)	23(1)
C(9)	3774(2)	7315(2)	11417(2)	27(1)
C(10)	5026(3)	6315(2)	11970(2)	47(1)
C(11)	4079(2)	9870(2)	12257(1)	23(1)
C(12)	4481(2)	11487(2)	13408(2)	31(1)
C(13)	5404(2)	12059(2)	14366(2)	29(1)
C(14)	5031(3)	12842(2)	14936(2)	49(1)
C(15)	5821(3)	13370(2)	15845(2)	59(1)
C(16)	6989(3)	13137(2)	16179(2)	45(1)
C(17)	7366(3)	12363(2)	15611(2)	48(1)
C(18)	6572(3)	11823(2)	14707(2)	45(1)
C(19)	7964(2)	11695(2)	11005(1)	28(1)
C(20)	7337(2)	12540(2)	11374(2)	26(1)
C(21)	6932(2)	12682(2)	12217(2)	30(1)
C(22)	6364(2)	13471(2)	12559(2)	35(1)
C(23)	6189(2)	14122(2)	12052(2)	36(1)
C(24)	6574(2)	13990(2)	11214(2)	35(1)
C(25)	7141(2)	13202(2)	10872(2)	31(1)

C(26)	4361(2)	11647(2)	8302(2)	30(1)
C(27)	4687(2)	12787(2)	8508(1)	26(1)
C(28)	3707(2)	13270(2)	8740(2)	32(1)
C(29)	3990(3)	14327(2)	8932(2)	43(1)
C(30)	5261(3)	14889(2)	8897(2)	46(1)
C(31)	6243(3)	14410(2)	8670(2)	46(1)
C(32)	5964(2)	13360(2)	8475(2)	34(1)
C(33)	5545(3)	9803(2)	6562(2)	34(1)
C(34)	4608(2)	9331(2)	5594(2)	31(1)
C(35)	3897(3)	9884(2)	5194(2)	43(1)
C(36)	3076(3)	9448(2)	4287(2)	48(1)
C(37)	2950(3)	8456(2)	3771(2)	42(1)
C(38)	3652(3)	7893(2)	4162(2)	41(1)
C(39)	4468(3)	8326(2)	5061(2)	38(1)
C(40)	6236(2)	8051(2)	7612(2)	28(1)
C(41)	6634(3)	6434(2)	7129(2)	34(1)
C(42)	5986(2)	6141(2)	6099(2)	30(1)
C(43)	6729(3)	6438(2)	5490(2)	41(1)
C(44)	6127(3)	6118(2)	4541(2)	48(1)
C(45)	4775(3)	5504(2)	4194(2)	41(1)
C(46)	4014(3)	5231(2)	4796(2)	42(1)
C(47)	4624(3)	5552(2)	5741(2)	38(1)
C(1A)	1113(2)	-356(2)	9808(1)	22(1)
C(2A)	1022(2)	667(2)	9699(1)	22(1)
C(3A)	110(2)	498(2)	8739(1)	22(1)
C(4A)	504(2)	-220(2)	7949(1)	23(1)
C(5A)	603(2)	-1195(2)	8160(1)	23(1)
C(6A)	-258(2)	-1740(2)	10185(1)	23(1)
C(7A)	-987(2)	-2706(2)	9362(2)	30(1)
C(8A)	-1009(2)	-1633(2)	10973(1)	24(1)
C(9A)	-1328(2)	-2615(2)	11209(1)	27(1)
C(10A)	-371(3)	-3712(2)	11844(2)	43(1)
C(11A)	-889(2)	-170(2)	12300(1)	23(1)
C(12A)	-588(2)	1234(2)	13649(2)	35(1)
C(13A)	481(2)	1888(2)	14529(2)	28(1)
C(14A)	681(3)	2940(2)	14854(2)	33(1)
C(15A)	1609(3)	3544(2)	15696(2)	39(1)
C(16A)	2339(3)	3106(2)	16222(2)	46(1)
C(17A)	2156(3)	2063(2)	15900(2)	47(1)
C(18A)	1236(3)	1455(2)	15061(2)	38(1)
C(19A)	3191(2)	1810(2)	10705(2)	31(1)
C(20A)	2588(2)	2551(2)	11300(1)	26(1)
C(21A)	2583(2)	3471(2)	11142(2)	33(1)
C(22A)	2029(3)	4160(2)	11687(2)	41(1)
C(23A)	1469(3)	3937(2)	12393(2)	50(1)
C(24A)	1473(3)	3029(2)	12554(2)	50(1)
C(25A)	2016(2)	2338(2)	12010(2)	36(1)
C(26A)	-373(2)	2118(2)	9084(2)	31(1)
C(27A)	-95(2)	3100(2)	8855(2)	24(1)
C(28A)	-16(2)	4002(2)	9546(2)	32(1)
C(29A)	209(3)	4926(2)	9371(2)	35(1)
C(30A)	339(2)	4958(2)	8497(2)	32(1)
C(31A)	263(2)	4067(2)	7804(2)	32(1)

C(32A)	52(2)	3138(2)	7983(2)	31(1)
C(33A)	-368(3)	95(2)	6525(2)	47(1)
C(34A)	-937(3)	-546(2)	5512(2)	33(1)
C(35A)	-283(3)	-1211(2)	5057(2)	44(1)
C(36A)	-766(4)	-1755(2)	4120(2)	57(1)
C(37A)	-1939(4)	-1664(2)	3623(2)	55(1)
C(38A)	-2632(3)	-1031(3)	4058(2)	53(1)
C(39A)	-2122(3)	-454(2)	5012(2)	42(1)
C(40A)	1176(2)	-1849(2)	7445(2)	28(1)
C(41A)	1744(2)	-3408(2)	7018(2)	30(1)
C(42A)	915(2)	-3859(2)	6019(2)	28(1)
C(43A)	1388(3)	-3535(2)	5326(2)	36(1)
C(44A)	627(3)	-3963(2)	4403(2)	45(1)
C(45A)	-595(3)	-4715(2)	4165(2)	42(1)
C(46A)	-1095(3)	-5038(2)	4852(2)	42(1)
C(47A)	-337(3)	-4613(2)	5776(2)	36(1)

Table 3. Bond lengths [Å] and angles [°] for 1.

O(1)-C(1)	1.408(2)	O(1)-C(5)	1.440(2)
O(2)-C(2)	1.427(2)	O(2)-C(19)	1.429(2)
O(3)-C(26)	1.422(2)	O(3)-C(3)	1.433(2)
O(4)-C(33)	1.431(3)	O(4)-C(4)	1.436(2)
O(5)-C(40)	1.428(3)	O(5)-C(41)	1.428(3)
O(6)-C(9)	1.205(3)	O(7)-C(9)	1.325(3)
O(7)-C(10)	1.448(3)	O(8)-C(11)	1.349(2)
O(8)-C(12)	1.447(3)	O(9)-C(11)	1.218(2)
O(10)-C(1)	1.407(3)	O(10)-C(6)	1.438(2)
O(16)-C(26A)	1.426(3)	O(16)-C(3A)	1.431(2)
O(1A)-C(1A)	1.414(2)	O(1A)-C(5A)	1.432(2)
O(2A)-C(2A)	1.419(2)	O(2A)-C(19A)	1.439(2)
O(4A)-C(4A)	1.427(2)	O(4A)-C(33A)	1.431(3)
O(5A)-C(40A)	1.423(3)	O(5A)-C(41A)	1.431(3)
O(6A)-C(9A)	1.207(3)	O(7A)-C(9A)	1.337(3)
O(7A)-C(10A)	1.452(3)	O(8A)-C(11A)	1.355(2)
O(8A)-C(12A)	1.452(3)	O(9A)-C(11A)	1.219(2)
O(10A)-C(1A)	1.407(2)	O(10A)-C(6A)	1.435(2)
N(1)-C(11)	1.342(3)	N(1)-C(8)	1.456(3)
N(1A)-C(11A)	1.342(3)	N(1A)-C(8A)	1.449(3)
C(1)-C(2)	1.523(3)	C(2)-C(3)	1.526(3)
C(3)-C(4)	1.514(3)	C(4)-C(5)	1.529(3)
C(5)-C(40)	1.501(3)	C(6)-C(7)	1.512(3)
C(6)-C(8)	1.534(3)	C(8)-C(9)	1.518(3)
C(12)-C(13)	1.499(3)	C(13)-C(14)	1.378(3)
C(13)-C(18)	1.377(3)	C(14)-C(15)	1.393(4)
C(15)-C(16)	1.372(4)	C(16)-C(17)	1.371(4)
C(17)-C(18)	1.389(3)	C(19)-C(20)	1.502(3)
C(20)-C(21)	1.394(3)	C(20)-C(25)	1.401(3)
C(21)-C(22)	1.391(3)	C(22)-C(23)	1.387(3)
C(23)-C(24)	1.379(4)	C(24)-C(25)	1.388(3)
C(26)-C(27)	1.505(3)	C(27)-C(28)	1.376(3)
C(27)-C(32)	1.388(3)	C(28)-C(29)	1.397(3)
C(29)-C(30)	1.378(4)	C(30)-C(31)	1.371(4)
C(31)-C(32)	1.387(3)	C(33)-C(34)	1.506(3)
C(34)-C(35)	1.384(3)	C(34)-C(39)	1.393(3)
C(35)-C(36)	1.389(4)	C(36)-C(37)	1.374(4)
C(37)-C(38)	1.381(4)	C(38)-C(39)	1.379(3)
C(41)-C(42)	1.510(3)	C(42)-C(47)	1.381(3)
C(42)-C(43)	1.386(4)	C(43)-C(44)	1.386(4)
C(44)-C(45)	1.381(4)	C(45)-C(46)	1.376(4)
C(46)-C(47)	1.382(3)	C(1A)-C(2A)	1.529(3)
C(2A)-C(3A)	1.536(3)	C(3A)-C(4A)	1.523(3)
C(4A)-C(5A)	1.528(3)	C(5A)-C(40A)	1.513(3)
C(6A)-C(7A)	1.516(3)	C(6A)-C(8A)	1.531(3)
C(8A)-C(9A)	1.515(3)	C(12A)-C(13A)	1.498(3)
C(13A)-C(18A)	1.391(3)	C(13A)-C(14A)	1.391(3)
C(14A)-C(15A)	1.387(3)	C(15A)-C(16A)	1.377(4)
C(16A)-C(17A)	1.381(4)	C(17A)-C(18A)	1.382(4)
C(19A)-C(20A)	1.502(3)	C(20A)-C(25A)	1.387(3)
C(20A)-C(21A)	1.394(3)	C(21A)-C(22A)	1.385(3)
C(22A)-C(23A)	1.381(4)	C(23A)-C(24A)	1.381(4)

C(24A)-C(25A)	1.381(4)	C(26A)-C(27A)	1.508(3)
C(27A)-C(32A)	1.383(3)	C(27A)-C(28A)	1.391(3)
C(28A)-C(29A)	1.387(3)	C(29A)-C(30A)	1.379(3)
C(30A)-C(31A)	1.382(3)	C(31A)-C(32A)	1.397(3)
C(33A)-C(34A)	1.504(3)	C(34A)-C(35A)	1.376(4)
C(34A)-C(39A)	1.381(4)	C(35A)-C(36A)	1.372(4)
C(36A)-C(37A)	1.368(5)	C(37A)-C(38A)	1.365(5)
C(38A)-C(39A)	1.405(4)	C(41A)-C(42A)	1.506(3)
C(42A)-C(43A)	1.381(3)	C(42A)-C(47A)	1.386(3)
C(43A)-C(44A)	1.389(3)	C(44A)-C(45A)	1.364(4)
C(45A)-C(46A)	1.384(4)	C(46A)-C(47A)	1.389(3)
C(1)-O(1)-C(5)	114.16(15)	C(2)-O(2)-C(19)	113.17(16)
C(26)-O(3)-C(3)	116.15(15)	C(33)-O(4)-C(4)	114.04(16)
C(40)-O(5)-C(41)	111.24(17)	C(9)-O(7)-C(10)	116.08(18)
C(11)-O(8)-C(12)	116.02(16)	C(1)-O(10)-C(6)	113.89(14)
C(26A)-O(16)-C(3A)	114.03(16)	C(1A)-O(1A)-C(5A)	113.86(15)
C(2A)-O(2A)-C(19A)	114.69(16)	C(4A)-O(4A)-C(33A)	116.02(16)
C(40A)-O(5A)-C(41A)	111.48(16)	C(9A)-O(7A)-C(10A)	115.72(18)
C(11A)-O(8A)-C(12A)	114.15(16)	C(1A)-O(10A)-C(6A)	115.19(14)
C(11)-N(1)-C(8)	120.59(17)	C(11A)-N(1A)-C(8A)	121.16(17)
O(10)-C(1)-O(1)	112.55(16)	O(10)-C(1)-C(2)	107.74(15)
O(1)-C(1)-C(2)	112.09(16)	O(2)-C(2)-C(1)	108.39(15)
O(2)-C(2)-C(3)	108.82(16)	C(1)-C(2)-C(3)	111.77(16)
O(3)-C(3)-C(4)	111.45(16)	O(3)-C(3)-C(2)	107.26(15)
C(4)-C(3)-C(2)	111.53(16)	O(4)-C(4)-C(3)	109.71(16)
O(4)-C(4)-C(5)	108.07(15)	C(3)-C(4)-C(5)	110.51(16)
O(1)-C(5)-C(40)	107.23(16)	O(1)-C(5)-C(4)	109.91(15)
C(40)-C(5)-C(4)	111.18(17)	O(10)-C(6)-C(7)	109.43(16)
O(10)-C(6)-C(8)	106.88(15)	C(7)-C(6)-C(8)	111.83(18)
N(1)-C(8)-C(9)	111.20(16)	N(1)-C(8)-C(6)	112.04(17)
C(9)-C(8)-C(6)	109.57(17)	O(6)-C(9)-O(7)	123.8(2)
O(6)-C(9)-C(8)	125.4(2)	O(7)-C(9)-C(8)	110.73(18)
O(9)-C(11)-N(1)	125.89(19)	O(9)-C(11)-O(8)	123.82(19)
N(1)-C(11)-O(8)	110.29(17)	O(8)-C(12)-C(13)	109.46(17)
C(14)-C(13)-C(18)	118.9(2)	C(14)-C(13)-C(12)	117.7(2)
C(18)-C(13)-C(12)	123.4(2)	C(13)-C(14)-C(15)	120.0(2)
C(16)-C(15)-C(14)	120.8(2)	C(15)-C(16)-C(17)	119.2(2)
C(16)-C(17)-C(18)	120.3(2)	C(13)-C(18)-C(17)	120.8(2)
O(2)-C(19)-C(20)	113.28(16)	C(21)-C(20)-C(25)	118.5(2)
C(21)-C(20)-C(19)	121.2(2)	C(25)-C(20)-C(19)	120.3(2)
C(22)-C(21)-C(20)	120.9(2)	C(23)-C(22)-C(21)	119.6(2)

C(24)-C(23)-C(22)	120.4(2)	C(23)-C(24)-C(25)	120.0(2)
C(24)-C(25)-C(20)	120.6(2)	O(3)-C(26)-C(27)	108.68(17)
C(28)-C(27)-C(32)	119.5(2)	C(28)-C(27)-C(26)	119.5(2)
C(32)-C(27)-C(26)	121.06(19)	C(27)-C(28)-C(29)	120.2(2)
C(30)-C(29)-C(28)	119.9(2)	C(31)-C(30)-C(29)	120.0(2)
C(30)-C(31)-C(32)	120.4(2)	C(31)-C(32)-C(27)	120.1(2)
O(4)-C(33)-C(34)	109.65(18)	C(35)-C(34)-C(39)	117.9(2)
C(35)-C(34)-C(33)	121.5(2)	C(39)-C(34)-C(33)	120.6(2)
C(34)-C(35)-C(36)	120.7(3)	C(37)-C(36)-C(35)	120.6(2)
C(36)-C(37)-C(38)	119.3(2)	C(39)-C(38)-C(37)	120.1(2)
C(38)-C(39)-C(34)	121.3(2)	O(5)-C(40)-C(5)	109.47(17)
O(5)-C(41)-C(42)	113.41(18)	C(47)-C(42)-C(43)	118.4(2)
C(47)-C(42)-C(41)	119.8(2)	C(43)-C(42)-C(41)	121.8(2)
C(42)-C(43)-C(44)	120.5(2)	C(45)-C(44)-C(43)	120.1(2)
C(46)-C(45)-C(44)	119.9(2)	C(45)-C(46)-C(47)	119.6(2)
C(46)-C(47)-C(42)	121.5(2)	O(10A)-C(1A)-O(1A)	112.91(15)
O(10A)-C(1A)-C(2A)	106.68(15)	O(1A)-C(1A)-C(2A)	111.99(16)
O(2A)-C(2A)-C(1A)	110.53(15)	O(2A)-C(2A)-C(3A)	107.59(16)
C(1A)-C(2A)-C(3A)	110.68(15)	O(16)-C(3A)-C(4A)	106.05(16)
O(16)-C(3A)-C(2A)	112.66(16)	C(4A)-C(3A)-C(2A)	111.87(16)
O(4A)-C(4A)-C(3A)	111.90(16)	O(4A)-C(4A)-C(5A)	105.58(15)
C(3A)-C(4A)-C(5A)	111.00(16)	O(1A)-C(5A)-C(40A)	106.60(16)
O(1A)-C(5A)-C(4A)	110.94(15)	C(40A)-C(5A)-C(4A)	111.43(17)
O(10A)-C(6A)-C(7A)	110.52(15)	O(10A)-C(6A)-C(8A)	106.25(15)
C(7A)-C(6A)-C(8A)	111.52(17)	N(1A)-C(8A)-C(9A)	111.95(16)
N(1A)-C(8A)-C(6A)	111.33(17)	C(9A)-C(8A)-C(6A)	110.38(16)
O(6A)-C(9A)-O(7A)	123.5(2)	O(6A)-C(9A)-C(8A)	124.8(2)
O(7A)-C(9A)-C(8A)	111.62(18)	O(9A)-C(11A)-N(1A)	125.53(19)

O(9A)-C(11A)-O(8A)	123.87(19)	N(1A)-C(11A)-O(8A)	110.60(17)
O(8A)-C(12A)-C(13A)	109.23(18)	C(18A)-C(13A)-C(14A)	118.8(2)
C(18A)-C(13A)-C(12A)	121.2(2)	C(14A)-C(13A)-C(12A)	119.9(2)
C(13A)-C(14A)-C(15A)	120.4(2)	C(16A)-C(15A)-C(14A)	120.3(2)
C(15A)-C(16A)-C(17A)	119.6(2)	C(18A)-C(17A)-C(16A)	120.5(2)
C(17A)-C(18A)-C(13A)	120.3(2)	O(2A)-C(19A)-C(20A)	113.34(17)
C(25A)-C(20A)-C(21A)	118.5(2)	C(25A)-C(20A)-C(19A)	121.2(2)
C(21A)-C(20A)-C(19A)	120.4(2)	C(22A)-C(21A)-C(20A)	120.8(2)
C(23A)-C(22A)-C(21A)	120.0(2)	C(22A)-C(23A)-C(24A)	119.5(2)
C(25A)-C(24A)-C(23A)	120.7(2)	C(24A)-C(25A)-C(20A)	120.5(2)
O(16)-C(26A)-C(27A)	109.42(18)	C(32A)-C(27A)-C(28A)	118.7(2)
C(32A)-C(27A)-C(26A)	122.9(2)	C(28A)-C(27A)-C(26A)	118.36(19)
C(29A)-C(28A)-C(27A)	121.0(2)	C(30A)-C(29A)-C(28A)	120.0(2)
C(31A)-C(30A)-C(29A)	119.5(2)	C(30A)-C(31A)-C(32A)	120.5(2)
C(27A)-C(32A)-C(31A)	120.2(2)	O(4A)-C(33A)-C(34A)	109.25(19)
C(35A)-C(34A)-C(39A)	118.7(2)	C(35A)-C(34A)-C(33A)	121.4(2)
C(39A)-C(34A)-C(33A)	119.9(2)	C(34A)-C(35A)-C(36A)	121.2(3)
C(37A)-C(36A)-C(35A)	120.2(3)	C(36A)-C(37A)-C(38A)	120.1(2)
C(37A)-C(38A)-C(39A)	119.9(3)	C(34A)-C(39A)-C(38A)	119.9(3)
O(5A)-C(40A)-C(5A)	108.67(17)	O(5A)-C(41A)-C(42A)	113.02(18)
C(43A)-C(42A)-C(47A)	118.7(2)	C(43A)-C(42A)-C(41A)	120.8(2)
C(47A)-C(42A)-C(41A)	120.4(2)	C(42A)-C(43A)-C(44A)	120.6(2)
C(45A)-C(44A)-C(43A)	120.5(2)	C(44A)-C(45A)-C(46A)	119.6(2)
C(45A)-C(46A)-C(47A)	120.1(2)	C(42A)-C(47A)-C(46A)	120.4(2)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2$ x 10^3) for 1. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U11 + ... + 2 h k a^* b^* U$

Atom	U11	U22	U33	U23	U13	U12
O(1)	26(1)	24(1)	21(1)	5(1)	2(1)	11(1)
O(2)	23(1)	23(1)	23(1)	4(1)	2(1)	2(1)
O(3)	26(1)	19(1)	35(1)	13(1)	-1(1)	5(1)
O(4)	25(1)	32(1)	19(1)	9(1)	3(1)	5(1)
O(5)	46(1)	22(1)	25(1)	4(1)	6(1)	13(1)
O(6)	34(1)	35(1)	59(1)	22(1)	11(1)	0(1)
O(7)	31(1)	35(1)	54(1)	28(1)	4(1)	7(1)
O(8)	25(1)	26(1)	28(1)	-3(1)	2(1)	7(1)
O(9)	23(1)	31(1)	29(1)	5(1)	3(1)	10(1)
O(10)	24(1)	20(1)	26(1)	11(1)	4(1)	7(1)
O(16)	36(1)	19(1)	28(1)	10(1)	10(1)	10(1)
O(1A)	25(1)	24(1)	20(1)	4(1)	2(1)	9(1)
O(2A)	24(1)	23(1)	27(1)	2(1)	3(1)	0(1)
O(4A)	34(1)	25(1)	20(1)	9(1)	-1(1)	3(1)
O(5A)	44(1)	23(1)	26(1)	8(1)	9(1)	15(1)
O(6A)	36(1)	36(1)	53(1)	16(1)	8(1)	-3(1)
O(7A)	37(1)	28(1)	40(1)	19(1)	2(1)	5(1)
O(8A)	26(1)	25(1)	26(1)	-1(1)	5(1)	5(1)
O(9A)	23(1)	33(1)	27(1)	7(1)	6(1)	11(1)
O(10A)	24(1)	20(1)	26(1)	8(1)	5(1)	7(1)
N(1)	19(1)	25(1)	22(1)	3(1)	0(1)	5(1)
N(1A)	19(1)	26(1)	22(1)	3(1)	2(1)	5(1)
C(1)	22(1)	24(1)	19(1)	6(1)	2(1)	7(1)
C(2)	19(1)	20(1)	23(1)	5(1)	4(1)	5(1)
C(3)	22(1)	18(1)	25(1)	8(1)	3(1)	4(1)
C(4)	21(1)	24(1)	21(1)	7(1)	1(1)	4(1)
C(5)	23(1)	23(1)	20(1)	4(1)	1(1)	6(1)
C(6)	28(1)	20(1)	24(1)	9(1)	5(1)	9(1)
C(7)	48(1)	21(1)	26(1)	6(1)	7(1)	5(1)
C(8)	19(1)	23(1)	23(1)	7(1)	2(1)	5(1)
C(9)	27(1)	28(1)	23(1)	7(1)	7(1)	6(1)
C(10)	52(2)	40(2)	63(2)	38(1)	10(1)	13(1)
C(11)	21(1)	26(1)	20(1)	7(1)	4(1)	5(1)
C(12)	28(1)	28(1)	33(1)	4(1)	5(1)	11(1)
C(13)	29(1)	24(1)	31(1)	7(1)	7(1)	7(1)
C(14)	51(2)	40(2)	45(2)	-4(1)	-1(1)	23(1)
C(15)	65(2)	46(2)	45(2)	-15(1)	-2(1)	25(2)
C(16)	41(2)	46(2)	29(1)	-4(1)	2(1)	6(1)
C(17)	36(1)	65(2)	34(1)	4(1)	0(1)	19(1)
C(18)	38(1)	54(2)	33(1)	-3(1)	3(1)	22(1)
C(19)	26(1)	25(1)	25(1)	4(1)	-2(1)	6(1)
C(20)	24(1)	22(1)	26(1)	4(1)	-1(1)	2(1)
C(21)	31(1)	29(1)	26(1)	10(1)	1(1)	3(1)
C(22)	36(1)	33(1)	26(1)	1(1)	3(1)	7(1)
C(23)	37(1)	24(1)	40(1)	2(1)	3(1)	7(1)
C(24)	39(1)	25(1)	39(1)	11(1)	3(1)	8(1)
C(25)	34(1)	25(1)	30(1)	9(1)	7(1)	5(1)
C(26)	30(1)	28(1)	32(1)	10(1)	0(1)	9(1)
C(27)	29(1)	27(1)	23(1)	10(1)	3(1)	10(1)

C(28)	28(1)	33(1)	33(1)	8(1)	5(1)	10(1)
C(29)	41(1)	32(1)	53(2)	7(1)	2(1)	18(1)
C(30)	46(2)	25(1)	61(2)	14(1)	-2(1)	10(1)
C(31)	39(1)	34(1)	66(2)	26(1)	6(1)	4(1)
C(32)	33(1)	31(1)	47(1)	19(1)	13(1)	13(1)
C(33)	38(1)	37(1)	25(1)	13(1)	11(1)	4(1)
C(34)	34(1)	37(1)	24(1)	15(1)	9(1)	8(1)
C(35)	58(2)	46(2)	34(1)	18(1)	14(1)	23(1)
C(36)	57(2)	65(2)	35(1)	27(1)	10(1)	28(2)
C(37)	40(1)	58(2)	25(1)	14(1)	5(1)	8(1)
C(38)	49(2)	36(1)	32(1)	5(1)	10(1)	8(1)
C(39)	42(1)	41(1)	33(1)	15(1)	7(1)	13(1)
C(40)	35(1)	20(1)	28(1)	6(1)	8(1)	8(1)
C(41)	43(1)	28(1)	28(1)	2(1)	2(1)	18(1)
C(42)	35(1)	25(1)	27(1)	4(1)	3(1)	14(1)
C(43)	35(1)	43(2)	41(1)	12(1)	7(1)	10(1)
C(44)	53(2)	62(2)	36(1)	21(1)	19(1)	18(1)
C(45)	53(2)	42(2)	25(1)	7(1)	5(1)	19(1)
C(46)	41(2)	38(2)	36(1)	7(1)	-3(1)	4(1)
C(47)	41(1)	38(1)	29(1)	9(1)	6(1)	5(1)
C(1A)	21(1)	21(1)	19(1)	3(1)	2(1)	4(1)
C(2A)	21(1)	21(1)	21(1)	4(1)	4(1)	4(1)
C(3A)	23(1)	16(1)	26(1)	8(1)	3(1)	3(1)
C(4A)	23(1)	21(1)	21(1)	6(1)	0(1)	3(1)
C(5A)	26(1)	19(1)	18(1)	3(1)	1(1)	3(1)
C(6A)	25(1)	22(1)	22(1)	9(1)	4(1)	9(1)
C(7A)	42(1)	21(1)	25(1)	7(1)	8(1)	9(1)
C(8A)	22(1)	22(1)	22(1)	4(1)	1(1)	5(1)
C(9A)	29(1)	27(1)	20(1)	3(1)	7(1)	3(1)
C(10A)	61(2)	30(1)	44(1)	24(1)	16(1)	12(1)
C(11A)	26(1)	23(1)	21(1)	9(1)	5(1)	8(1)
C(12A)	33(1)	33(1)	36(1)	4(1)	13(1)	13(1)
C(13A)	34(1)	25(1)	26(1)	7(1)	11(1)	9(1)
C(14A)	42(1)	29(1)	28(1)	7(1)	13(1)	15(1)
C(15A)	48(2)	27(1)	36(1)	1(1)	18(1)	9(1)
C(16A)	49(2)	48(2)	28(1)	1(1)	4(1)	9(1)
C(17A)	58(2)	50(2)	35(1)	17(1)	3(1)	20(1)
C(18A)	49(2)	28(1)	40(1)	11(1)	13(1)	13(1)
C(19A)	26(1)	22(1)	35(1)	1(1)	-4(1)	3(1)
C(20A)	22(1)	23(1)	25(1)	5(1)	-3(1)	0(1)
C(21A)	35(1)	26(1)	31(1)	7(1)	4(1)	2(1)
C(22A)	39(1)	24(1)	50(2)	1(1)	1(1)	8(1)
C(23A)	39(2)	48(2)	40(1)	-15(1)	4(1)	8(1)
C(24A)	43(2)	63(2)	27(1)	4(1)	7(1)	-4(1)
C(25A)	33(1)	39(1)	28(1)	12(1)	-2(1)	-1(1)
C(26A)	34(1)	26(1)	39(1)	15(1)	15(1)	12(1)
C(27A)	21(1)	24(1)	30(1)	11(1)	4(1)	8(1)
C(28A)	39(1)	33(1)	29(1)	12(1)	10(1)	15(1)
C(29A)	47(1)	24(1)	35(1)	7(1)	9(1)	14(1)
C(30A)	38(1)	24(1)	38(1)	15(1)	12(1)	11(1)
C(31A)	42(1)	30(1)	31(1)	15(1)	11(1)	14(1)
C(32A)	36(1)	25(1)	31(1)	7(1)	7(1)	10(1)
C(33A)	71(2)	31(1)	30(1)	15(1)	-4(1)	2(1)

C(34A)	42(1)	30(1)	23(1)	11(1)	5(1)	1(1)
C(35A)	55(2)	41(2)	43(1)	19(1)	13(1)	17(1)
C(36A)	87(2)	44(2)	41(2)	11(1)	26(2)	16(2)
C(37A)	78(2)	45(2)	23(1)	7(1)	9(1)	-8(2)
C(38A)	43(2)	74(2)	38(1)	34(2)	-1(1)	-4(1)
C(39A)	46(2)	56(2)	36(1)	27(1)	17(1)	16(1)
C(40A)	36(1)	22(1)	25(1)	7(1)	7(1)	8(1)
C(41A)	38(1)	25(1)	28(1)	4(1)	6(1)	16(1)
C(42A)	33(1)	23(1)	29(1)	4(1)	6(1)	15(1)
C(43A)	39(1)	33(1)	32(1)	6(1)	9(1)	6(1)
C(44A)	55(2)	47(2)	28(1)	9(1)	8(1)	12(1)
C(45A)	49(2)	42(2)	26(1)	-1(1)	-2(1)	15(1)
C(46A)	37(1)	33(1)	45(1)	4(1)	-2(1)	6(1)
C(47A)	37(1)	32(1)	37(1)	11(1)	8(1)	7(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for 1.

Atom	X	y	z	U(eq)
H(1)	5598	9298	12064	29
H(1A)	667	-601	11946	29
H(1B)	6629	9605	10549	27
H(2)	5515	10874	10316	26
H(3)	4215	10130	8786	26
H(4)	6686	10072	8128	27
H(5)	4653	8339	8231	28
H(6)	5493	8023	10425	28
H(7A)	2787	7279	9202	49
H(7B)	3480	6564	9647	49
H(7C)	4157	7041	8936	49
H(8)	2957	8304	10903	27
H(10A)	4494	6264	12442	71
H(10B)	5983	6340	12215	71
H(10C)	4611	5716	11404	71
H(12A)	3531	11191	13458	37
H(12B)	4443	11962	13046	37
H(14)	4235	13020	14708	59
H(15)	5548	13899	16239	71
H(16)	7531	13506	16797	53
H(17)	8173	12195	15835	58
H(18)	6839	11286	14320	53
H(19A)	8972	11995	11100	33
H(19B)	7832	11219	11369	33
H(21)	7045	12234	12562	36
H(22)	6098	13565	13136	42
H(23)	5800	14661	12284	43
H(24)	6452	14438	10870	42
H(25)	7398	13111	10292	37
H(26A)	3504	11390	8492	36
H(26B)	4216	11298	7622	36
H(28)	2834	12883	8771	39
H(29)	3308	14658	9086	52
H(30)	5458	15609	9030	55
H(31)	7118	14800	8647	55
H(32)	6649	13033	8319	41
H(33A)	6384	9565	6577	40
H(33B)	5838	10558	6730	40
H(35)	3971	10570	5543	52
H(36)	2598	9839	4021	58
H(37)	2385	8160	3152	50
H(38)	3573	7207	3810	49
H(39)	4944	7930	5323	45
H(40A)	5801	7985	6966	33
H(40B)	7244	8372	7731	33
H(41A)	6575	5802	7294	41
H(41B)	7626	6806	7252	41
H(43)	7658	6863	5726	49
H(44)	6645	6322	4129	57

H(45)	4370	5271	3542	49
H(46)	3076	4824	4562	51
H(47)	4094	5363	6153	46
H(1AA)	1818	-212	10397	26
H(2A)	618	1024	10202	26
H(3A)	-876	191	8733	27
H(4A)	1415	137	7865	28
H(5A)	-338	-1599	8158	27
H(6A)	717	-1752	10427	27
H(7A1)	-1899	-2666	9091	44
H(7A2)	-1098	-3302	9576	44
H(7A3)	-442	-2773	8888	44
H(8A)	-1911	-1520	10739	28
H(10D)	-933	-3712	12306	64
H(10E)	534	-3779	12096	64
H(10F)	-841	-4290	11269	64
H(12C)	-1367	800	13800	42
H(12D)	-955	1674	13336	42
H(14A)	178	3260	14497	39
H(15A)	1743	4262	15912	46
H(16A)	2966	3520	16803	55
H(17A)	2666	1761	16259	56
H(18A)	1118	739	14846	46
H(19C)	4121	2184	10679	38
H(19D)	3303	1290	11003	38
H(21A)	2963	3627	10655	39
H(22A)	2035	4785	11574	50
H(23A)	1083	4405	12765	60
H(24A)	1098	2878	13045	60
H(25A)	1999	1711	12122	44
H(26C)	34	2264	9755	37
H(26D)	-1383	1804	8959	37
H(28A)	-118	3985	10147	39
H(29A)	275	5537	9853	42
H(30A)	479	5587	8372	38
H(31A)	356	4086	7202	39
H(32A)	8	2531	7503	37
H(33C)	622	463	6632	56
H(33D)	-875	608	6699	56
H(35A)	518	-1296	5398	53
H(36A)	-284	-2196	3815	69
H(37A)	-2271	-2043	2975	65
H(38A)	-3459	-980	3716	64
H(39A)	-2591	0	5312	50
H(40C)	629	-1985	6806	33
H(40D)	2148	-1486	7490	33
H(41C)	1869	-3971	7254	37
H(41D)	2673	-2985	7040	37
H(43A)	2242	-3016	5482	43
H(44A)	961	-3729	3934	54
H(45A)	-1100	-5016	3530	51
H(46A)	-1957	-5549	4693	51
H(47A)	-679	-4842	6258	43